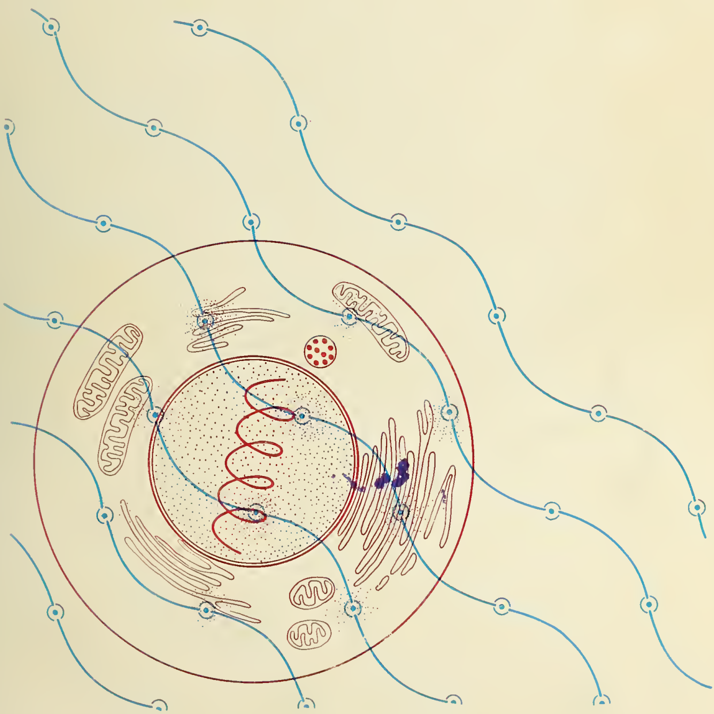
An Atlas of Radiation Histopathology

by *David C. White, M. D.*



Technical Information Center, Office of Public Affairs
U. S. ENERGY RESEARCH AND DEVELOPMENT ADMINISTRATION

TID-26676

An Atlas of Radiation Histopathology

David C. White, M. D.

Chief, Division of Radiation Pathology
Armed Forces Institute of Pathology
Washington, D. C.

1975

Published by
Technical Information Center
Office of Public Affairs
U. S. Energy Research and Development Administration

Library of Congress Cataloging in Publication Data

White, David Craig, 1924-
Atlas of radiation histopathology.

"TID-26676."
1. Radiation—Toxicology. 2. Histology, Pathological.
3. Cancer—Radiotherapy—Complications and sequelae. I. Title.
[DNLM: 1. Radiation injuries—Pathology—Atlases. 2. Radiotherapy—Adverse effects—Atlases. WN17 W583a]
RA1231.R2W48 611'.018 75-17867
ISBN 0-87079-019-X

Available as TID-26676 for $7.60 (foreign, $10.10) from

National Technical Information Service
U. S. Department of Commerce
Springfield, Virginia 22161

ERDA Distribution Category UC-48

Printed in the United States of America
USERDA Technical Information Center, Oak Ridge, Tennessee

June 1975

Preface

Ionizing radiation has become a highly effective means of combating cancer. In many forms of this dread disease, therapeutic irradiation, as the sole definitive treatment, has been capable of controlling or substantially retarding the spread of the malignancy. In certain circumstances both primary and metastatic growths have been destroyed.

The characteristics that endow ionizing radiation with its remarkable tumoricidal propensities at the same time cause damage to nontumorous tissues within the radiation field which can eventuate severe patient distress and disability. The nature of the response of these organized tissues is regulated by innumerable factors, inherent and conditional, each tissue type reacting according to a pattern determined largely by the relative radiosensitivities of its diverse, integrated cell populations. The times from exposures at which these often clinically significant responses become evident and the ways in which they adversely affect the health and well-being of the patients are of considerable interest and importance to the therapeutic radiologist since these parameters often control dose limitation in treatment planning.

Some tissues are capable of manifesting early syndromes reflecting rapidly developing decrements in one or more of their principal cell populations. Generally these tissues are structurally and functionally dependent on rapid-cell-renewal populations that can incur prompt and dramatic injury from doses in the therapy range often within hours or days after exposure. Although such tissues comprise only a relatively small proportion of the body's total cell mass, they are frequently responsible for individual patient morbidity. The severe patient distress associated with acute exudative radiation pneumonitis, ulcerative gastritis or enteritis, and ulcerative dermatitis and mucositis attests to the potential dangers that can relate to inappropriate exposures of certain body regions.

The ultimate expression of this prompt compromise of the more radiosensitive cell populations is seen in the various debilitative and potentially lethal syndromes associated with whole-body irradiation.

On the other hand, most tissues have principal cell populations that respond more slowly to radiation. Individual cells within the irradiated tissues are affected randomly in relation to both response time and distribution, thereby allowing for repair of sublethal cell damage and institution of compensatory mechanisms. An early injury phase in these tissues may be subclinical but capable of initiating changes that will be progressive and become manifest months to years later. This delayed radiation pathology is frequently insidious in its development, the late clinical syndrome often surfacing unexpectedly as either a spontaneous event or associated with some relatively minor unrelated stress.

The efficacy of the multimodal approach to cancer therapy, with the extraordinary advances in surgical techniques, the encouraging results of chemotherapy, and the outstanding improvements of radiation sources with refinements in modes of application, is reflected in a steadily expanding survival of an increasing proportion of treated patients. This brightening prospect is somewhat clouded by persistent and, in some respects, increasing incidences of delayed damage in exposed critical body tissues and the consequent debilitative, even lethal, sequelae.

The enhanced possibility of extended patient survival has placed greater importance on the individual tolerance with respect to these late-developing radiation-related sequelae and the diversity of associated syndromes. It becomes imperative that those individuals responsible for the application of radiation in cancer therapy and those who must

evaluate the subsequent tissue responses have a practical comprehension of the pathogenesis and histopathologic characteristics relating to the direct and indirect actions of this agent.

Radiation pathology in the broad sense is concerned with the identification, investigation, and evaluation of those changes produced in the diverse cell populations of the body by the direct or indirect actions of ionizing radiation. From the practical point of view, however, the principal thrust of this publication is directed at those lesions severe enough to be capable of causing significant functional or structural decrements in body systems that may adversely affect the individual's health. This atlas, however, is not intended to be a comprehensive treatise of the many and complex facets of radiation pathology. It is, in effect, a visual histopathologic exercise and makes no pretense of considering, in any detail, the many factors, e.g., genetic, immunologic, and metabolic, which may be closely interrelated to the pathogenesis of the tissue alterations.

It is therefore the fundamental purpose of this atlas to briefly delineate and describe those morphologic effects which are associated with the actions of ionizing radiation in diverse tissues and to correlate those observations with the physiological constitution of the involved tissue, certain physical characteristics of the applied radiation, and the times through which specific responses develop.

The materials used have been selected from the teaching files of the Registry of Radiation Pathology, a component of the American Registry of Pathology. These cases come from Armed Forces medical installations, Veterans Administration hospitals, U. S. Public Health Service, Atomic Energy Commission, and civilian contributors.

The literature referenced omits many excellent publications. The chapter bibliographies include those articles and books used in the review of specific subject matter, and it is from this diversity of selected background information that the text of this atlas has been devised.

A subject index has not been included in view of the outline format and purposeful abbreviation of the text. The photomicrographs and descriptive captions that comprise the major element of this atlas hopefully illustrate most of the lesions associated with the irradiation of specific organs and tissues. Certain organs and tissues have not been included or have been given more or less cursory treatment because of insufficient or inadequate material, case documentation, and information.

If there is disagreement on the part of my colleagues with some of the concepts or criteria, this is as it should be in a field of investigation that is changing so rapidly. Even as this manuscript was in preparation, new or revised views on fundamental radiobiology and radiation pathogenesis were being established or proposed.

I wish to thank the many colleagues who urged me to develop a visual reference for radiation histopathology and who provided advice and encouragement during the preparation of this atlas.

I am indebted to the Director and Staff of the Armed Forces Institute of Pathology for their understanding and cooperation and am particularly grateful to the members of the Medical Illustration Services for their support in the production of the photomicrographs and illustrations. Luther Duckett and Ralph Eisenberg were especially helpful in this regard.

I wish to acknowledge with appreciation the secretarial assistance of the staff of the Department of Radiologic Pathology and secretarial service of the Institute. Particular thanks go to Michelina Bowen for her diligence and devotion in the compilation and summarization of references and careful typing and organization of the manuscript.

I am most grateful for the kindness of the staff of the Technical Information Center, Energy Research and Development Administration, who have given so generously of their time and effort to see this task completed.

Most of all, I wish to commend my wife, Pat, and our children, Cheryl, David, Richard, and Diane, for their patience and tolerance during the preparation of this atlas.

David C. White, M. D.

Contents

Chapter 1
Acute Whole-Body Irradiation

INTRODUCTION

Many excellent publications have contributed to the understanding of whole-body irradiation and its clinical and pathological implications. Most of them fall into basic categories with regard to context and scope. Of first consideration are the factual case reports concerning those infrequent instances of inadvertent, excessive whole-body exposure in humans (Table 1.1). Most of these reports are concise and contain as much dosimetric, clinical, and pathological data as was available and considered pertinent at the time of the incident. The more recent reports have included excellent reviews of previous overexposures correlating, insofar as possible, the clinical stages and tissue damage with dose absorbed and time after irradiation.

Closely related to these instances of accidental overexposure are the many more or less controlled clinical investigations into specific aspects of human responses to irradiation of the total body or a major portion thereof. A considerable portion of this human material is derived from the irradiation of patients whose variable physical states make interpretation of the observed effects difficult at best. Because of the sparsity of pertinent and valid human data, there is often augmentation by information derived from analyses of other mammalian species with limited comparisons of specific biological parameters. A third source of information, and by far the most voluminous, concerns comprehensive experimental studies of total-body irradiation based wholly upon the reactions of a very broad spectrum of animal species. The inherent factors of uncertainty associated with attempted extrapolations of animal responses to those of humans make careful consideration of these data imperative. This in no way implies an underrating of the stature of these animal experiments. They have always been the foundation upon which much of the knowledge of human radiation injury has been based.

The term total-body irradiation as applied to a specific type of exposure and as used in this volume is far more often than not inaccurate in its implication.

It is difficult, even under the most stringent of laboratory conditions, to approach a condition whereby all tissues of the body are subjected to a uniform field of ionizing radiation. There may be many factors controlling the degree of homogeneity of any given exposure, e.g., the directional nature of the radiation, the orientation of the body with respect to this radiation, the characteristics of the radiation, and the presence of interposed materials producing some degree of shielding or attenuation.

For practical purposes, therefore, total-body irradiation should apply to the exposure of a major portion of the body, including the trunk and head, to penetrating ionizing radiations of sufficient energies to transect all tissues within the field without requisite uniformity of dose.

It is obvious that the entity commonly referred to as total-body irradiation syndrome cannot be taken in the strict literal sense. It refers to a complex of biological decrements produced when the major portion of the body is exposed to an effective level of radiation. Assignation of accurate total-dose values to specific body segments or organs is virtually impossible except in carefully controlled laboratory animal experiments, whole-body radiation therapy, and unplanned exposures where it is possible to determine the exact attitude of the individual in relation to the source of radiation. Furthermore, there is no reliable clinical indicator, such as the visible epidermal demarcation of thermal burns. The erythema associated with ionizing radiation is inconsistent, dose dependent, and related to the character of the radiations.

The time factor of acute whole-body irradiation must also be considered. Through what period of time do the resultant biological decrements act to affect the health and survival of the exposed individual? It is reasonable to assume that the kinetics of radiation injury activate at the instant of energy transferral and that the sequence of many biological changes are amplified and develop promptly. In a matter of minutes to hours both clinical and histological manifestations may become apparent in high-dose exposures. The time it takes this acute injury to evolve and then regress is largely dependent upon the total dose absorbed and the time over which it is administered. It is recognized that the clinical response to such an acute exposure may be identified over an expanded period of several weeks but that beyond this it is difficult to characterize the illness solely on the basis of the direct effects of radiation upon critical body systems. Laboratory analyses on the other hand may reflect specific radiation-induced defects for a much more protracted period of time. Exactly where the terminus of the acute radiation syndrome, as a defined entity in man, is would be largely conjectural and cannot

Table 1.1

	Case A	Case B	Case C	Case D	Case E
Age	38	38	32	26	35
Type of accident	Pu recovery process	^{235}U recovery process	Critical assembly (experimental)	Critical assembly (experimental)	Reactor excursion
Dose (total body estimate)	900 rads neutron, 4000 rads gamma	2200 rads neutron, 6600 rads gamma	2000 R 80 kV X ray, 110 rads gamma	480 R 80 kV X ray, 110 rads gamma	320 rads neutron, 320 rads gamma
Survival	35 hr	49 hr	9 days	25 days	32 days
Immediate symptoms	Ataxia; disorientation	Abdominal pain; headache; nausea	Nausea	Nausea	None
Vomiting	Severe, 15–20 min	Severe, 5–10 min	Moderate, 1 hr	Severe, 1½ hr	Moderate, 1 hr
Diarrhea	Severe, 45 min	Severe, 10 min (bloody-?)	Once, 4 hr	None	3rd day
Hypotension	Prompt, severe; 30 min	Severe, 3–4 hr	Mild, 14 hr	Mild, 24 hr	None
Erythema (onset)	Almost immediate	Almost immediate	24 hr	3 days	8–10 hr
Fever	Peak, 103.6°F, 3 hr	Peak, 102°F, 17 hr	Moderate and irregular; terminal, 105°F	Progressive to death; terminal, 106+°F	?
Leukocytosis	28,000 in 12 hr; 14,000 terminal	46,000 in 38 hr; (last count)	18,000 in 24 hr; marked terminal leucopenia	16,000 in 24 hr; marked terminal leucopenia	11,000 in 24 hr
Lymphocytes	0–10 hr	1% in 15 hr; 0 in 21 hr	Near 0 in 24 hr	Near 0 in 48 hr	Near 0 in 5 days
Latent period	2nd to 28th hr	10th to 36th hr	1st to 6th day	Not recognizable	3rd to 21st day
Death	Cardiovascular; ? CNS	Cardiovascular	Intest. obstr.; circulatory failure	Toxemia	Intest. obstr.; renal failure

be satisfactorily extrapolated from experimental mammalian exposures.

The syndrome that is produced by whole-body irradiation is one of extreme complexity. The number of factors and combinations of these factors which may affect the nature of the biological responses to radiation are so numerous as to stagger the imagination. Those which are recognized as playing a major role in the development of the acute radiation syndrome have been subjected to exhaustive investigation. To consider any one of these in any detail far exceeds the intended scope of this text. In addition, many less well-defined factors still require extensive study for adequate interpretation, and limitations of present analytical methods have been the principal deterrent to the resolution of many of these problems. There are undoubtedly other interacting factors as yet undiscovered or identified in theory only which remain to be explored.

What pathological developments are necessary to produce the composite clinical picture recognized as the acute whole-body irradiation syndrome?

The transmittal of energy from penetrating radiations to the cells and substances of the body is accomplished primarily by ionization and excitation of the molecular structure. These processes, which involve the basic biochemical composition, produce alterations in critically balanced molecular states. Depending upon the magnitude of these changes and the compensatory capacities of the molecular systems involved, the resultant defect may be promptly rectified or may be biologically amplified. This enhanced injury may in some manner affect the functional or structural integrity of the cell or substance.

The smallest unit within the body bearing characteristics both morphological and functional which set it aside as a member of a defined population or system is the mature or differentiating principal parenchymal cell. It is true that there are many intracellular or subcellular macromolecules and organelles; however, more often than not, these may be readily identified as components of almost all cells and are concerned with common, nonspecific functions relating to the life process of an individual cell. In general, the macromolecules and organelles do not have variable characteristics which would identify them per se with related organ or body functions. Each cell type will respond in characteristic fashion to the stress imposed by radiation.

For many years, the basis for the derivation of relative sensitivity of mammalian cells to radiation was the generalization that increased sensitivity was related to the mitotic activity, regenerative rate, and relative state of the differentiation of the cell. This so-called law of Bergonie and Tribondeau was founded upon a series of excellent rodent studies and was defensible up to a point. Many recognized exceptions to this law have been developed, but the generalizations still hold true in most cases. At this point in the genesis of radiation injury, therefore, the type of cell affected and its inherent cytokinetics become of great importance to the establishment of its pattern of response. In the adult individual, three categories of cells are identified by cytokinetics:

1. Those cell types which proliferate during the rapid-growth phases of the embryonic and neonatal periods and

then lose their capacity for regeneration. These are the nonproliferative cells.

2. Those cells which under normal conditions or circumstances of limited stress exhibit little or no proliferation but which in special situations of extreme stress or demand may develop a wave of cell divisions which is transient in nature. These are classified as conditionally proliferative cells.

3. The proliferative cell types which because of their specific functions in the body are expendable and are therefore subject to continuous attrition. These cell types must be continuously replenished throughout the functional life of the tissue or organ of which they are the principal component.

If any radiation defect develops in one of the nonproliferative or conditionally proliferative cell populations whose function within the body is of little concern to the basic "life processes" of the individual, the biological amplification will be restricted primarily to the individual cell and will usually in no way compromise the structure or function of the tissue of which it is a component part. For example, the random production of damage among the striated-muscle cells may be of protracted evolution, and, because there is no mitotic demand upon this cell, the passage of time may allow restitution of much of the defect. Even considering sufficient injury to produce cell death, the remaining functional cells readily compensate for the decrement unless a large proportion are affected. Moreover, when cell deaths occur in such postmitotic systems, they are random in both location and time distribution.

In contrast, the evolution of radiation injury in cells of the proliferative type will result in a dramatically different sequence of events. The tissues or organs of which these cells are the principal components require constant cell renewal for the maintenance of proper function. Generally, this function is vital to the well-being of the individual as a whole.

The rapid-renewal cell types have short generative cycles and are very reactive during the sensitive portions of these cycles even at relatively low doses; therefore, most of the prompt cell damage is related to the numerous mitoses. The response times of these susceptible proliferative cells may be so abbreviated as to invoke severe depletion of the affected population before regenerative efforts become effective.

Basic Cytokinetics

There are three composite biological systems within the body whose relative compromise determines the majority of deaths from acute whole-body irradiation. Of these, two represent rapid-renewal cell systems, hematopoietic and gastrointestinal, and the third, the central nervous system, is of the nonproliferative group in which there is no reproductive replacement of the principal parenchymal cells in the adult. A cell-renewal system is simply a specific population of cells having a common progenitor cell in which the loss of cells from whatever cause is balanced by the production of equal quantities of new cells. For any such system to function, it must have precursor or progenitor cells whose primary purpose is to continue to regenerate its kind. In the mucosa of the small intestine, this is accomplished by the proliferation of cells in the midportion of the crypt epithelium. In the bone marrow, it becomes the function of the earliest myeloblast or erythroblast elements. In addition, there must also be a self-sustaining source of undifferentiated or uncommitted stem cells. The concensus is that there is not a single omnipotent cell that supplies the renewal requirements of the entire body but that there are numerous basic forms of stem cells, each one being specific by its genetic composition for one or more particular cell lines within the diverse renewal systems of the body. Under unstressed circumstances, these stem cells are in a steady-state equilibrium wherein they continue to reproduce their own kind at a set rate with a certain ratio of the daughter cells showing differentiation and continuing on a separate course to become progenitor cells of particular cell species. Although the stem cell has not been positively identified morphologically and its relative radiosensitivity has not been accurately determined, its presence has been established by a large amount of experimental evidence. Any stress or demand imposed upon this steady-state condition within the stem-cell household results in an acceleration of the regenerative activity of this stem-cell population and a greater proportion of the daughter cells differentiating for potential development into specific cell types.

Statistically when a stem cell divides, half the progeny should be identical with the parent cell and the remaining half should show differentiation into the specific cell line (Fig. 1.1). Whether or not this is actually the case has not been satisfactorily determined. In general, however, once the destiny of these precursor cells has been determined by the first indications of cell specificity, then they undergo a transitional period of further division and additional differentiation. The successive stages of maturation probably occur primarily in the intermitotic phases of this period, which may consist of one to several successive divisions before the cell enters the mature, nonproliferating cell population, where it then assumes the functional obligation for which it was destined at the time of earliest differentiation.

Probably the most efficacious adjunct to the study of cell-population kinetics came with the development of radionuclide-labeled compounds and more specifically tritiated thymidine (^{3}H–TdR). Thymidine is a precursor substance that is metabolized into DNA. Incorporation by those cells actively developing DNA occurs with extreme rapidity following the introduction of this substance into the nutritive system be it in vivo or in vitro. This material is readily identifiable within these cells by means of high-resolution autoradiography. This process permits the critical evaluation of a specific generation of cells by means of serial sampling following the progression of events from this point of DNA synthesis to cell loss by attrition or other means. This technique has provided a relatively simple means of determining not only the duration of the various phases of the generative cycle but also the biological life of the cell during the time that it is a functional unit of the system and, for that matter, the body as a whole.

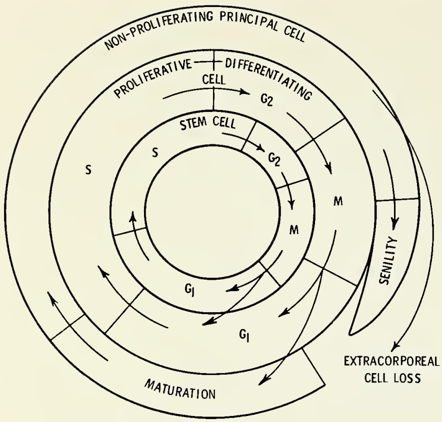


Fig. 1.1 Cell generation, differentiation, maturation, and attrition.

Certain histopathological observations are important to the consideration of the acute bone-marrow response:

1. The stem cells are radiosensitive to a degree, in that their total numbers and/or proliferative capacities are reduced following exposure to relatively small amounts of radiation.

2. The most immature of the differentiating progenitor cells would appear to be the most sensitive of those cells in the proliferative compartment of the marrow. They are drastically reduced in number by the actions of ionizing radiation, either through prompt cell death or by delayed cell death connected with induced mitotic abnormalities. The depression of this proliferative cell pool is also enhanced by the failure of the stem cells to promptly provide additional differentiating progenitor cells. As the cell types pass through the series of divisions and progressive maturation, their responsiveness to irradiation decreases; therefore, proportionally fewer cells of this type would be destroyed at any given exposure.

3. Those cells which have undergone changes both morphologically and functionally as a result of abnormal mitoses may continue to survive in an atypical state and through some mechanism are permitted to enter the general circulatory pool.

4. As in all systems of rapid cell renewal, the action of radiation induces a period of mitotic inhibition in the proliferative compartment. The duration of this period of suppression is partially dependent upon the magnitude of the radiation dose. Mitotic activity, however, reappears within several hours at moderate doses, although many of these mitoses may now be abnormal.

5. The mature cells of any of these series are resistant to the actions of radiation in the doses practical for consideration. Their time of survival, if they were in this stage at the time of irradiation, appears little altered from that of the normal value.

6. It is the depletion of the formed elements occurring as a result of this failure of renewal which produces the indirect sequelae responsible for death in the hematologic syndrome, e.g., infection, hemorrhage, and anemia.

It has been assumed that the stem cells during the early phases of regeneration are regulated through some demand mechanism of the body to undergo homomorphogenic divisions; that is to say that the daughter cells are also primarily stem cell in nature. It is also assumed that the first requirement in this initial period of acute stress is probably to reestablish some sort of pool or compartment of stem cells before a signal is received to feed-in an increasing percentage of daughter cells showing the first stages of differentiation into the hematopoietic progenitor cells. It is further assumed that, once the renewed feed-in process from the stem-cell population has achieved the desired replenishment of the proliferative portion of the hematopoietic system, this process of exaggerated stem-cell division reverts to the more steady state of self-replenishment with steady feed-in. The exact nature of the mechanism responsible for governing this orderly regenerative process of the hematopoietic system has not been identified.

The pattern of response which holds true for the hematologic system is similar to that followed by the small intestine in the gastrointestinal syndrome, one very important difference being that the stem cells of the proliferative region of the intestinal crypts show evidence of being less responsive to the actions of ionizing radiations than those of the hematopoietic system. Experimental evidence indicates that a larger dose of acutely administered radiation is required to produce significant functional damage or death in the stem cells. Within 48 to 72 hr following irradiation, the crypts and the villi may be entirely lined by a greatly diminished population of atypical cells that are the result of mitotically connected injury. The block of cell division induced by the radiation in the proliferative zone of the crypt is of longer duration than that seen in the bone marrow. However, this is speaking in relative terms because of the larger dose required to produce this mitotic inhibition in the intestinal tract as opposed to the lesser dose that will bring about a similar response in the bone marrow.

In contrast to the hematologic syndrome, it is not the direct loss of the cells and cell products which produces the death; it is the secondary changes brought about by denudation and ulceration of the intestinal mucosa. Therefore, electrolyte and fluid imbalance are the principal bases for death in the gastrointestinal syndrome, infection and nutritional debilitation being probable contributory factors.

The central nervous system syndrome does not have mitotic arrest as the basic provocation of events contributing to death. There are no dividing parenchymal cells within the central nervous system and no stem-cell pool that is recognized as such.

Whatever sequelae arise as a result of intensive irradiation in the head region must, therefore, be an effect upon the neurons or their synapses produced by the direct action of ionizing radiation or mediated through changes related to the vascular response. This results in rather

inconsistent sequelae, such as severe ataxia, convulsions, hypotension, and a shock-like condition progressing to coma.

CLINICAL CORRELATION

Over the years, it has been considered useful to establish a basis for comparison of the lethal responses in the various animal species under different conditions of irradiation. This value has become known as the $LD_{50/30}$ value and represents the magnitude of radiation at which there will be 50% fatality among exposed individuals over a 30-day postirradiation period. The 30-day standard was not arbitrarily selected but was the result of experience that showed that most animals receiving substantial whole-body irradiation will die from the acute effects of this agent within 30 days. This figure has had to be modified for man to $LD_{50/60}$ to include the extended survival in man of those individuals having incurred sufficient injury to the hematopoietic system to result in death during this additional 30-day period. The severe hematopoietic decrement still falls within the category of an acute direct lethal effect. There are two other possible levels of comparison which would be of value in the triage of multiple radiation casualties; one would be the dose at which death would occur in 100% of the exposed individuals within a span of 24 to 48 hr, and the second would be that dose below which no deaths would be expected during the initial 60-day interval. In both these latter instances, the degree of individual variability apparently precludes the establishment of any practical definitive value. Those deaths which occur in the latter portion of the prescribed acute radiation syndrome period (60 days in man; 30 days in other animal species) are rather clearly defined as being due to the depletion of the formed blood components. Those individuals receiving a higher total dose who died at earlier times in the acute postexposure condition have somewhat less well defined modes of death in that intermediate states develop in which there is significant injury to both the intestinal mucosa and the hematopoietic tissue and it is often difficult to determine which, if either, is producing the primary defect. A similar situation exists for those individuals receiving excessively high doses where certain of the symptoms suggest central nervous system (CNS) compromise but there is also extensive injury of the intestinal mucosa, the hematopoietic tissues, and the microvasculature. Serious consideration must be given, therefore, to the probability that multiple factors contribute significantly to the very early deaths that are so often ascribed to CNS injury alone.

There is, in fact, increasing evidence that there may be a fourth "syndrome" that becomes dominant at dose levels between the CNS and intestinal syndromes. This implies that the generally accepted levels for the production of true central nervous system responses should be raised to about 10,000 R. The basic defect in the broad range of 3000 to 6000 R may be associated with the microvascular system. Many effects could be ascribed to relative and variable ischemia produced by swollen endothelial and smooth-muscle cells in the capillaries and precapillaries and by compromise of the vascular barrier with outpouring of fluid and formed blood components.

The problem of inhomogeneous exposure in the so-called whole-body irradiation syndrome has become a subject for considerable conjecture when the areas of the body receiving the bulk of the radiation can be rather well defined as to specific anatomical regions. If this is carried to extremes and that portion of the body irradiated, for example, the head, the thorax, or the abdomen, is sharply limited, an entirely new set of values develops insofar as lethality is concerned, although the signs and symptoms are comparable in some respects to those associated with the various syndromes of total-body irradiation. For example, when single doses of 1500 to 2000 R are given to the head region alone, the delayed death is primarily associated with changes developing within the oropharynx. This has been often referred to as "oral death." In contrast, when the dose administered is increased by a factor of 3 or greater, the clinical manifestations become similar in some respects to those ascribed to the CNS syndrome as it has been identified with total-body irradiation. Irradiation of the thorax alone does not produce a well-defined syndrome of any type, although a significant depression in hematopoietic activity may be an early sequela. On the other hand, when the region of the abdomen is irradiated separately with single doses in the range of 1000 to 1500 R, a syndrome results which is similar in many respects to that associated with the intestinal death of the total-body irradiation. It becomes apparent that any irradiations where more or less of these body zones are included within the beam will produce a diversity of effects that do not follow any set pattern. This is the basis, therefore, for considering total-body irradiation to be the inclusion of a major portion of the total body volume, more specifically, the abdomen, thorax, and head.

From the standpoint of triage of casualties and from a prognostication point of view, it has been considered practical to further clinically categorize individuals exposed to whole-body irradiation. This classification is dependent upon the total dose absorbed but is characterized by certain signs and symptomatology displayed by the individuals involved. Those persons irradiated can, therefore, be divided into the following groups:

1. Those exposed individuals in which there are no anticipated deaths and where survival is almost a certainty.
2. Those individuals where death is possible, but survival is expected.
3. Those severely injured persons where death is probable, but survival is possible if adequate medical care is applied.
4. Finally, those excessively exposed where the outcome is essentially 100% lethal.

In the last category, we find that, with the greatest magnitude of exposure, ataxia, disorientation, confusion, and hypotension occur immediately, and an irreversible shock-like state develops rapidly. There are prompt vomiting, watery stools, and severe cramping abdominal pains. If the amount of absorbed radiation is somewhat less, the dramatic neurogenous decrement and early refractive hypotensive state diminish. The appearance of prompt nausea

and vomiting persists, the diarrhea becomes more frequent with associated dehydration and ionic imbalance, and there is again abdominal distress, but this latter symptom now occurs late in the brief clinical course and usually after a variable but short latent period of relative well being. Prompt erythema may develop. In the more heavily irradiated individuals in this category, death will occur within several days preceded by clinical responses and signs relating primarily to a severe pancytopenia, such as localized and systemic sepsis, hemorrhagic diatheses, and anemia.

The next most severe category is that in which the radiation damage has been extensive but survival is possible. Here, again, nausea and vomiting occur promptly. There is not, however, the concurrent symptomatology that is related to the central nervous system. All the individuals in this group experience a sense of fatigue; in some instances, the fatigue regresses over the following several days, but in most it will persist for prolonged periods of time. There is variable abdominal discomfort. Hematopoietic depression, which begins between the 5*th* and 10*th* days, becomes dominant and increases rather rapidly. There is an initial granulocyte depression, with an associated increased susceptibility to the actions of microorganisms. As the leucocyte and thrombocyte values continue to decline over the subsequent several days, there are further evidences of poorly controlled infections, e.g., ulcerative stomatitis, urinary-tract infections, ulcerations of the intestinal tract, tonsillitis, and pharyngitis. Appearing at the same time may be hemorrhagic manifestations, such as petechiae, purpura, epistaxis, and gingival hemorrhage. It becomes obvious that this is an extremely critical period in this particular category of exposure. A severe infection in any locus of the body at this time could expand virtually unchecked with fatal consequences. The prolongation of survival time in this category permits the appearance of epilation during the 3*rd* to 4*th* weeks after exposure. It is also in this general classification that the exact region of the body receiving the greatest burden of radiation becomes a determining factor in the severity of the general debilitation and the potential for survival. Frequent hemograms become a means of evaluating the overall condition of the individual and usually manifest the following sequential changes:

1. Prompt granulocytosis during the first few days after exposure represents mobilization of the mature granulocyte pool in marrow and possibly spleen probably in response to the initial widespread cell degeneration.
2. A decline in total leukocytes to below normal values.
3. The slope of this cell-population curve tends to level off and in some instances actually rebounds toward normal during the second week after irradiation.
4. During the 4*th* and 5*th* weeks, this temporary remission is interrupted by the resumption of the leukopenic process.
5. Recovery from this cell depression, if it is to occur, will commence at this time.
6. The lymphocytes, in contrast to the granulocytes, exhibit a prompt and dramatic depression reaching the minimum value in 3 to 4 days, and the level remains very low with recovery slow and variable.
7. The depression of the thrombocyte population continues at a relatively slow but steady pace with minimum values attained about the 5*th* week after exposure; the recovery phase begins in 7 to 10 days and precedes or parallels the total leukocyte response.

In the category where death is a possibility but survival is expected, there is usually an initial stage of nausea sometimes accompanied by vomiting, and diarrhea of slight to moderate degree may occur later. The hematologic depression is the principal response of concern although it is not so severe as in the categories previously described. In other words, the reserve defense mechanism of the body is not as severely compromised, and intercurrent infections and hemorrhagic tendencies become less hazardous to the irradiated individual. If treatment is inadequate or virulent microorganisms invade the body, then death will become a distinct possibility. Most of these individuals exhibit a loss of vitality and increased fatigability with an associated anorexia and general malaise. Some hemorrhagic manifestations may be apparent during the 4*th* to 5*th* weeks but with much less severity than in the more heavily irradiated category. The pancytopenia follows a pattern similar to that already described, but the depression is not so severe. Rapidly developing lymphocytopenia may be an exception.

In the group where survival is expected, clinical manifestations of the exposure may be entirely lacking or of a minimal nature, and there is little or no consistency in the symptoms that have been recorded. Often the only means of determining the presence of any significant degree of injury is an evaluation of the peripheral blood, which will show variable depression of most of the formed components.

HEMATOPOIETIC SYSTEM

Cytokinetics of Bone-Marrow Cell Renewal

The marrow has several characteristics that make it unique from other cell-renewal systems within the body. First, the marrow does not exist as an anatomical unit unto itself; that is, it is a richly vascular, loosely bound tissue within which is a highly efficient cell factory producing those formed elements of the blood required by the body. This hematopoietic tissue is encased within the rigid confines of certain of the bones. In the young individual almost all the bones of the body contain productive marrow. In the mature human, however, this active marrow becomes localized to the sternum, the ribs, the vertebrae, and the ilium. The primary purpose of the marrow is hematopoiesis, and three distinct cell species make up the hematopoietic system. These cell types exist together in more or less random distribution although there is a tendency toward species congregation by virtue of retention of progeny within circumscribed areas. This gives some credence to one of those inexplicit and inconsistent axioms of histopathology which states that a cell may often be identified by the company it keeps. The three cell species that comprise hematopoiesis are myelopoietic, erythropoietic, and thrombopoietic. An additional feature of interest and one not fully explained is that even under

conditions of uncommon stress or disease, the immature and proliferating elements of the erythropoietic and thrombopoietic systems are seldom seen outside the confines of the marrow, whereas immature components of the myelopoietic series are not infrequently identified in the peripheral blood under such circumstances.

The requirements of the body for specific mature and functional formed elements of the blood place definitive demands on the appropriate cell-species renewal system. This will be reflected in the cytologic composition of the marrow and its degree of deviation from the cell ratios associated with an unstressed state, which is why periodic marrow and peripheral blood studies are used as a means of determining the capacity of the hematopoietic tissue to perpetuate the mature cell populations required by the body for proper function.

With regard to the specific injurious effects of ionizing irradiation upon this tissue, the basic element of interest is the degree of compromise of the specific stem cells. The difficulty in evaluating this critical prognostic parameter persists as a major problem in the assessment of damage incurred by this organized tissue. It becomes necessary, therefore, to rely mainly upon the evaluation of those cells within the hematopoietic system flowing through the circulating system which are readily identifiable by careful cytologic evaluation.

Subdivision of the hematopoietic cells into morphologically distinct stages of development is largely of academic interest in constructing patterns of relative cell responsiveness. Such a categorization for hematokinesis and cell-type responsiveness to the stress of irradiation is seen in Fig. 1.2. Any such classification based upon subjective interpretation of a progression of cytological alterations must, of necessity, be more or less arbitrary even when performed by an experienced hematologist. Moreover, highly discriminatory subdivision serves no particularly useful purpose in the practical analysis of tissue response.

On the other hand, such a categorization makes it possible to recognize the immature and proliferating elements as a development phase of the hematokinesis and serves as a gauge of the injury–repair cycle.

In the hematopoietic tissues, however, one cannot consider a single cell-type transit time as can be done with the intestinal or seminiferous epithelia. Each of the three cell series comprising the hematopoietic tissue of the marrow has specific characteristics that set it apart. The limits of the individual transit times, therefore, may be clearly defined and should be concerned only with those cell stages having clear cytologic definition.

For example, although there is little doubt as to the existence of a stem cell, the kinetics of this most primitive cell form is for the most part unknown and precludes its employment in any assessment of cell development time.

At the opposite extreme of cell development, the time span of functional maturity is somewhat more amenable to evaluation but even so is usually subject to a wide swing of time values. For practical purposes cell life-span should begin at the time of first perceptible indication of cell differentiation and extend to the termination of functional efficacy. This end point may be sharply defined, as in the intestinal epithelial cell as it sloughs from the villus tip; it

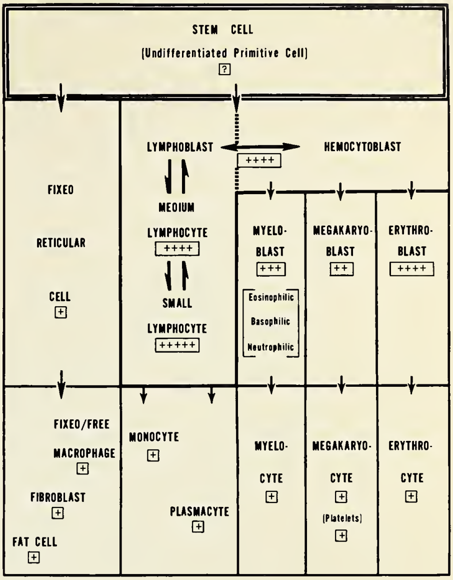


Fig. 1.2 Hematopoiesis and relative radiosensitivity.

may be subject to a more or less narrow range of values, as in the senescent degeneration of granulocytes, erythrocytes, and platelets; or the destiny may be almost totally unpredictable, as in the degeneration of the mature sperm as a functional unit, which may occur within the male genital system or within a female genital system many hours and many miles distant.

The critical periods of time which it takes for specific cell types to proceed from the earliest point of differentiation in the progenitor cells to the terminus of the fully matured nonproliferative functional cells, therefore, will vary for the different cell lines concerned within the same individual and will also vary among different species of animal. Therefore, the heavy reliance upon studies of the radiation effect in animals and the possible extrapolation of these results to man must take into account the fact that experience has shown this transit time from cell division to the mature state to be more rapid in the small animal species than in the larger animal species. Much has been accomplished in determining the relative state of deficiency subsequent to irradiation, the period through which this deficiency is in effect relative to the dose absorbed, and those measures which may be employed to offset this deficiency if only on a temporary basis.

Effects of Radiation on Hematopoietic Tissues and Blood

That extensive cytologic abnormalities develop in the marrow cells subsequent to irradiation has been shown by

innumerable excellent studies encompassing many species of animals. A general observation has been that the alterations that occur are similar in all species with differences in degree of response and in the time through which the individual changes occur (Fig. 1.3). During the first few hours immediately following the irradiation, a wave of cell death occurs primarily in the immature proliferating components and especially in those which were in the more sensitive phases of their generative cycles at the time of the insult. The debris from these disrupted cells as well as from cells severely injured and dying is promptly engulfed and removed by the phagocytic cells rapidly mobilized in the marrow. The initial mitotic suppression induced by the radiation is eased several hours after the exposure and is marked by an abundance of cell divisions some of which are abnormal in composition. This brief mitotic surge is followed by the appearance of numerous abnormal cell forms in the marrow which are the products of radiation-induced mitotic aberrations. These atypical cells may die promptly or survive for brief periods of time in a state of functional impairment. Some may succeed in entering and even completing subsequent atypical or abortive efforts at cell division. Some of the more persistent forms of cytologic abnormalities observed include nuclear swelling; multipolar mitoses; mitoses exhibiting chromosomal fragmentation, chromosome stickiness, and chromosomal bridging; giant cells with either a single enlarged nucleus or multiple distorted nuclei; cells containing karyomeres or cytoplasmic clumps of chromatin material; and other cells showing nuclear fragmentation.

It should be noted that there is a strong likelihood that the vast majority of immature cell forms in the marrow have been damaged in some manner and, therefore, will manifest either a structural or a functional defect or both. This defect may not appear until the first postirradiation division is attempted, at which time it may prevent initiation or completion of the mitosis or produce abnormal daughter forms. If the injury is not so severe, two or more successive mitoses may be accomplished before all the daughter cells succumb to the lethal nature of the original radiation defect or there is sufficient revision of the defect to permit extended cell survival. A certain number of marrow cells, however, will have sustained minimal injury and the resultant alteration will not inhibit mitosis nor will it be transmitted to the daughter cells, or the injury may be either totally or partially resolved with no compromise of subsequent cell generations. It is also probable that a certain statistical proportion of the cells may incur no injury whatsoever.

One aspect of the response of the hematopoietic tissues to radiation which has not been adequately explained is the initial and prompt elevation of the peripheral granulocytes subsequent to relatively high doses. This has been observed in several animal species as well as in man. There is a strong likelihood that it reflects a response to the widespread cell degeneration in the diverse rapid cell-renewal systems throughout the body by the pool of mature granulocytes present in the bone marrow and to some degree in the spleen and in the capillary and sinusoidal beds of the body. Its relationship to the magnitude of dose received lends some credence to the contention that it is a systemic reaction to the degenerative products of the widespread cell destruction.

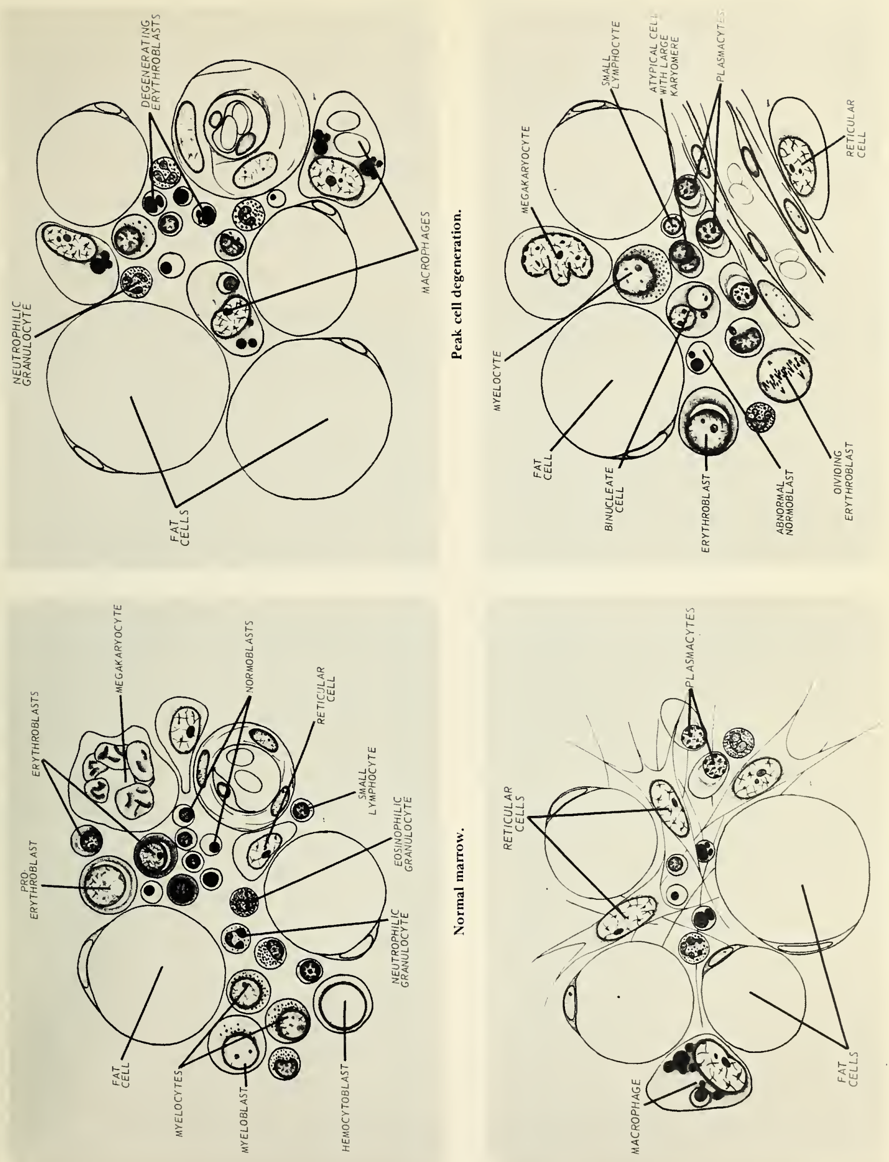
The response of the small lymphocyte to irradiation is a significant component of the peripheral nucleated-blood-cell picture. This cell type will be considered in detail later. There is some tendency to relegate the small lymphocyte to a relatively unimportant status insofar as its impact upon the body as a whole. This may be due in large part to the fact that the development cycle of the lymphocyte is not fully understood and the function of the lymphocyte within the body is even less well defined. The contention is that, although the small lymphocyte is one of the most radiation-responsive cells of the body, widespread degeneration of this particular cell population appears to have limited significant bearing upon subsequent debilitation or survival of the exposed individual. Some investigations have indicated that the function of the lymphocyte may vary according to the site of origin and point of residence within the body. There is also some indication that it is primarily through the death and dissolution of the lymphocytes that materials which provide important DNA and other substances to developing cells are disseminated and that lymphocytes also may possess the potential of becoming instrumental in reactions against antigenic substances. A great deal of investigation is still necessary to fully evaluate this particular cell because there is now evidence that under certain stimulation the cells do not necessarily remain in their so-called mature form but may have the capacity to revert to a more primitive form of cell with the potential for differentiating along other specific morphological and functional lines. The very severe and very prompt depression of the small lymphocyte population subsequent to irradiation and the rather slow reappearance in the peripheral blood over an extended period of time might indicate that the specific progenitor cell of the lymphocyte is particularly sensitive to ionizing radiation and may undergo a change that prevents or delays an enhanced regenerative phase, or that the stem cell may be called upon to program its production along an entirely different line of cell differentiation. At this point, there is no convincing evidence in support of any of these contentions, and the origin, action, and fate of the lymphocytes must remain as one of those enigmas requiring extensive investigation.

As with most of the rapid cell-renewal systems, the sequence of histopathologic events following irradiation will be similar regardless of species. The relationships of the kinetic patterns to dose and time, however, will exhibit considerable variation.

Myelocytic

An initial granulocytosis may persist for hours or possibly days followed by a rapid depression of the granulocytic population. The degree of this decline and the time after exposure at which the minimum value is attained are largely functions of dose and mammalian species involved.

Those progenitor cells in a particularly sensitive portion of the generative cycle are severely damaged. The more immature the cell, the greater this response. Many of the cells in this proliferative compartment will be prevented



Normal marrow.

Peak cell degeneration.

Hypocellular marrow.

Hematopoietic regeneration.

Fig. 1.3 Bone marrow.

from initiating cell division for several hours or more and then, because of injury, be unable to complete a normal mitosis. If atypical cell division is achieved, the progeny are generally abnormal in both structure and function. It is likely that they are incapable of further division or maturation and will undergo early degeneration or persist for variable periods as nonfunctional abnormal cells. Some of these initial abnormal cell forms may appear in the peripheral blood at about the time of minimal population and persist until the abortive recovery.

Depending upon the dose absorbed, a proportion of this proliferative compartment may have sustained minimal or no injury and continue to divide and mature in an essentially normal fashion.

Those cells in the nonproliferative compartment at the moment of exposure are significantly less sensitive to the actions of the radiation, and their maturation processes will be little, if at all, affected. The subsequent life-span and function of these cells do not appear to be appreciably altered.

The abortive rise, which may occur from 5 to 30 days after the irradiation, is variably present in the myelocytic, erythrocytic, and megakaryocytic series. The mechanism of this abortive rise has not been satisfactorily defined, but it seems reasonable to assume that it primarily concerns the alarm response of the stem-cell compartment. The diversity of hypotheses that have been propounded to explain this temporary recovery is evidence of the relative deficiency in understanding some of the basic principles of cell renewal in the marrow. The most plausible explanation for this response is also the least complex in terms of postulating variance of structure and function. It is reasonable to assume that at the moment of irradiation the stem cells incur the same proportionate injury as all other cells within the same field. As with all other cell compartments, therefore, there are three degrees of effect: stem cells destroyed outright, cells injured but capable of resuming limited cell division after the release of the radiation-induced block, and cells receiving minimal or no injury which, by the time the functional block is released, are fully capable of assuming the responsibilities of a challenged stem-cell component. The abortive rise reflects the resumption of mitosis by the second group along with some divisions from the third category.

The postulation of changes in feedback signals or stress-initiated trigger responses directed at the stem-cell pool deserves mention. Although it is unlikely that this alone could explain the abortive rise, such a mechanism could operate in conjunction with the first theory. With very high doses, this abortive rise may be minimal and difficult to identify. The granulocytopenia appears at about 2 to 3 weeks, remains profound, and is largely responsible for essentially unopposed intercurrent infection.

Sustained granulocytic regeneration begins after the abortive rise has reverted to low levels, although, in some circumstances of moderate radiation, the two responses may not be sharply separated. The time of onset is from several days to 3 weeks after the irradiation depending upon the magnitude of the absorbed dose. The pattern of this recovery is largely a reflection of the efficacy of that portion of the stem-cell compartment which sustained little or no damage.

Erythrocytic

Because radiation does not significantly alter the functional attributes and longevity of the mature erythrocyte, the values of this particular cell form are not likely to change radically following exposure. Even with doses of lethal and supralethal magnitude, anemia becomes a problem primarily on the basis of hemorrhage.

The relatively inconspicuous response in the peripheral erythrocyte component, however, does not accurately reflect the dramatic changes that have occurred in the erythropoietic series of the marrow. This response is similar in most respects to that observed for the myelocytic series.

The immature proliferative cells are reputedly slightly more sensitive than those of the myelocytic type and are readily damaged by relatively low doses of radiation and exhibit an immediate and sharp depression with the maximum acute effect attained in about 24 hr. The marked sensitivity to irradiation and the inherent short transit time in the marrow seem to be major factors in the obvious paucity of persistent abnormal forms in the marrow in contrast to the commonplace presence of atypical myelocytes.

The nondividing maturing nucleated erythrocytes are relatively resistant to the action of the radiation and are present in the marrow for the duration of a normal transit time.

As a gauge of erythrocyte attrition successive hematocrit values are preferable to the red-cell count because the latter can be altered by changes in plasma volume. Reticulocyte evaluations essentially parallel the values for myelocytes, exhibiting the same abrupt drop, abortive rise, and subsequent sustained recovery which may develop over a period of several weeks or longer.

Megakaryocytic

Because there is no cell division beyond the "blast" stage, as such, in the megakaryocytic series but rather nuclear division and overall cell enlargement, it is difficult to quantitate the early response to radiation. If nuclear characteristics are taken as a measure of maturity, however, the so-called megakaryoblast, a relatively small cell with a single regular or folded nucleus, disappears rapidly from the marrow and the multinucleated mature forms persist for extended periods after irradiation.

The decline in megakaryocytes is linear after an initial shoulder, and the acuteness of the slope and minimum value are dose and species dependent. This depletion of the megakaryocytes is more or less based upon a normal attrition rate with little or no cell replacement.

The platelets exhibit a related depression, as would be expected. Although the platelets under normal circumstances are formed by the fully mature megakaryocyte, under conditions of stress they may be derived from more immature cells. Minimum levels in man are attained in 3 to 4 weeks with an LD_{50} value.

Summary

The principal functional component of the marrow is the hematopoietic tissue, which can be further categorized into three cell systems, myelopoietic, erythropoietic, and thrombopoietic.

In all three systems the primary functional unit, i.e., segmented granulocyte, erythrocyte, and thrombocyte (platelet), is nonproliferative and in itself is not particularly sensitive to radiation. Each has vital duties that concern the physical state of the individual. The primary effect of radiation on these systems is to compromise the precursor pool and thereby arrest cell replacement.

Each system responds in a somewhat different manner based upon specific cytokinetics.

1. Myelopoiesis—transit time in marrow, 8 to 10 days. There is a large component of proliferating cells that are sensitive to radiation.

2. Erythropoiesis—transit time in marrow, 4 to 6 days. The proliferating forms are even more sensitive than those in the myelocytic series. This condition coupled with the relatively short transit time produces very rapid depletion of this cell species in the marrow.

3. Thrombopoiesis—transit time of the megakaryocyte 4 to 10 days. Cell division occurs only in the progenitor "blast" form, which is radiosensitive. The maturing megakaryocytes are not as responsive to radiation as the other two cell types; however, damage to the dividing nuclei may produce severe cell injury.

The life-spans of the mature radioresistant units become of prime importance in determining the nature of the impending cell decrement and the time at which this particular damage will become so severe as to affect the prognosis of the irradiated individual.

The granulocytes, with a life-span in the circulation of only hours to 1 or 2 days, become rapidly depleted and, thereby, deprive the body of a major defense against systemic infection.

The erythrocyte with an extended life-span of 109 to 127 days exhibits no dramatic depression and, therefore, plays no direct role in the debilitation of the irradiated individual. It should be pointed out, however, that any loss of blood from hemorrhage will not be replenished until such time as renewal of erythropoiesis resumes.

The thrombocyte has a life-span of only 8 to 9 days in the peripheral blood but is not immediately affected because of the protraction of the megakaryocyte response. Only the earliest progenitor form undergoes immediate lethal changes. Most of the remaining megakaryoctyes, though damaged, will continue some degree of maturation and some will be capable of limited platelet production. This provides a slowly diminishing source of platelets.

Relation to Infection

One of the principal secondary effects of the pancytopenia induced by radiation is an increased susceptibility to infection. Under carefully monitored treatment conditions where precautions against contamination by virulent organisms can be maintained at a high level, this secondary sequela can be kept to a practical minimum. Unfortunately, where there may have been excessively high doses to a particular segment of the body in addition to the overall whole-body irradiation, unusually severe defects may develop in certain protective biological barriers which will become evident at about the same time that the pancytopenia is at or near its maximum depression. These may take the form of denuded areas of irradiated skin, ulcerations of the mucous membranes, focal epithelial denudation of the air passages as well as potential defects within the alveoli themselves. Those humans accidentally exposed to sublethal and lethal quantities of radiation have not shown the same bacteremia that has been evident in so many animal experiments. This inconsistency may have more than one plausible explanation. First, many of the victims of Hiroshima and Nagasaki developed lethal bacteremias owing to the poor or nonexistent prophylaxis against intercurrent infection. Second, it may be that there is a species difference as to predisposition for the development of bacteremia, and, finally, it may be simply that means of detecting bacteremia in man are not sufficiently accurate. This latter contention has support in the fact that autopsy specimens exhibiting widespread bacterial growth have failed either premortem or postmortem to produce positive blood cultures. It has also been shown experimentally that antibiotics may significantly alter the lethality in heavily irradiated animals.

The effect of whole-body irradiation on the defenses against potentially pathogenic microorganisms deserves detailed consideration. The body possesses a composite of mechanisms which act to efficiently eliminate microorganisms from the circulation and to isolate these organisms and cause their destruction. The initial response sees the majority of organisms filtered from the circulation by the action of the reticuloendothelial cells of the liver and spleen as well as the lymph nodes. These organs are particularly efficient by virtue of the numerous fixed macrophages. This is not a simple process of entrapment by these cells but is the product of the interplay of several factors, among them being (1) certain components in the serum which appear to be requisites for this type of phagocytic activity, (2) certain specific immune substances and (3) the type of organism, which is an important factor with regard to the avidity with which it is engulfed. It is difficult, if not impossible, to overload the capacity of the reticuloendothelial structures for microbial filtration. In addition to the organs already indicated, it is likely that the circulating granulocytes themselves play a role in the clearance of bacteria from the circulation. Granulocytes are known to adhere to the walls of the capillaries and then to engulf the circulating microorganisms. There is unfortunately not an entirely clear picture of what transpires following this initial clearance from the blood of the microorganisms. As pointed out, these invading bacteria are engulfed by the macrophages of the reticuloendothelial system, especially in the spleen, liver, and lymph nodes and in certain of the capillary beds. At this point, there appears to be some interacting mechanisms that in some way determine the manner and the degree in which these invaders will be destroyed. In some instances the entire invading population will be neutralized and disposed of; however, in other instances foci of these organisms will

continue to multiply in the locations where they have been phagocytized and isolated. There is no full understanding of what determines this eventual fate. Some factors that have been mentioned are various forms of intercurrent stress, such as shock, circulating endotoxin, and pancytopenia, or, more specifically, an agranulocytopenia or certain debilitating states of the body, such as profound metabolic or nutritional states.

In the particular condition observed with whole-body irradiation of a clinically significant magnitude, there appears to be no particular decrement in the ability of the phagocytes to engulf the microorganisms. However, there does seem to be a deficiency in their capacity for destroying these organisms. This might be suspected from the experience of finding certain deficiencies in the immunological structure of the body subsequent to irradiation. This point at which the lytic capacities of the cells are retarded or nullified coincides with the greatest degree of granulocytopenia noted in the peripheral-blood hemogram. Whether there is a direct relationship between the two states is not known. It is possible that there is a substance contained within the granulocyte which when released promotes the destruction of the ingested bacteria. It must be concluded, therefore, that, although there may exist a radiation-induced granulocytopenia, those reduced numbers of mature granulocytes which are mobilized and become localized in an area of microorganismal invasion retain the capacity for ingestion and immobilization of these organisms.

Ionizing radiation can produce anatomical defects in the efficient barriers of the mucous membranes, the skin, and the mucosa of the gastrointestinal tract. These will provide exaggerated portals of entry for microorganisms. It should be noted that even under essentially normal conditions small numbers of bacteria may invade the body across the apparently intact membrane and these bacteria are capable of culture from regional reticuloendothelial structures. It seems logical to conclude, therefore, that the combined factors of greater facility of entry and a lessened capacity for bacteriolysis combine to produce the severe sequela of bacteremia in irradiated individuals. Decreased mobility of the phagocytic cells has also been cited as one possible reason for lessened resistance; however, it would seem from most experiments that exceptionally high doses of radiation are required to produce such an effect.

Certain aspects of antibody formation are severely depressed even by relatively low doses of radiation. The primary immune response is the most sensitive; the secondary response is relatively radioresistant. With commensal organisms, such as those from the gastrointestinal tract, the secondary response is predominant, whereas with pathogens the primary response is predominant. Animals usually die within 2 to 4 days after infection or bacteremia develops, and this represents a period of time which is generally considered insufficient for antibody formation to play any significant protective role. Immunized animals given a sublethal exposure retain a resistance to the appropriate organism; however, this protective effect dissipates when radiation doses in the lethal or supralethal range are administered. These protective antibodies would appear to be active only in the presence of specific cellular elements, and at the time of severe granulocytopenia this particular defense mechanism of the body is not fully functional. The following comment from a monograph by V. P. Bond, T. M. Fliedner, and J. O. Archambeau summarizes this problem: "Defense of the normal individual against infection depends upon the integrity of a number of factors including the reticuloendothelial system, antibody production, the bactericidal power of the serum and the presence of neutrophils. All of these appear to be impaired to some degree following massive exposure to radiation. The evidence is overwhelming, however, that the principal defect leading to infection following massive exposure to radiation is the neutropenia. Impairment of other defence mechanisms appears to merely modify or be dependent upon this primary defect. The degree to which the modifying factors assume importance undoubtedly will vary depending upon the host, the source of the infection, and the infective agent."

Certain generalizations may be made:

1. Irradiated individuals are more susceptible to infection than nonirradiated individuals.
2. This susceptibility is primarily the result of the developing pancytopenia and specifically granulocytopenia.
3. Radiation-induced defects in the protective barriers of the body offer portals of entry coinciding with this granulocytopenia.
4. There is probably a significant compromise of certain facets of the immunological defense mechanisms of the body.
5. For the preceding reasons, a localized infection could rapidly develop into a generalized bacteremia.
6. Antibiotics may play a significant role in the therapy of this infection if the period of severe hematopoietic depression is relatively brief.

Relation to Bleeding Diathesis

Thrombocytes are vital to the production of effective coagulation. They have a dual role in this respect in that both a biochemical factor and a physical factor are present in the formation of the clot. Support is given to this contention by the fact that transfusions of fresh thrombocytes during a period of hemorrhagic diathesis result in a rather dramatic reconstitution of the capacity for clot formation. Further support for the relationship between the thrombocytopenia and the hemorrhage is that in intense localized radiotherapy over predetermined areas of the body there is no evidence of any significant hemorrhage or petechiae formation. This same quantity of radiation, however, similarly administered but at a time when there is a severe thrombocytopenia will provoke a hemorrhagic response. This is not to be considered a consequence of capillary fragility but is rather the production of defects in the capillary or endothelial barrier with resultant extravasation of red cells which in the presence of adequate numbers of thrombocytes would be avoided.

During the period of symptomatology primarily referable to the pancytopenia, there are also apparent signs and symptoms associated with the gastrointestinal tract.

Among these are diarrhea, which may be bloody at times, abdominal cramping and pain, anorexia, and weight loss. It is probable that these effects are largely the products of interaction between a poorly reconstituted intestinal mucosa and a combined granulocytopenia and thrombocytopenia with the development of ulcerative and bleeding lesions, ineffectively controlled by the normal defense mechanisms of the body. The manifestations of the hemorrhagic syndrome are variable according to the species involved. For example, clinically significant anemia is very common in the irradiated rodent species and in the rabbit but not quite so prevalent in man or in some of the larger mammalian species. In man, the primates, dog, and swine, gross hemorrhage is not uncommon, whereas in the smaller mammalian species, rodents in particular, gross hemorrhage is minimal, but a great deal of extravasation of erythrocytes out into the tissues and bleeding into the gastrointestinal tract occur. Regardless of the mode of red-blood-cell loss, it may in any event be sufficient to produce a severe anemia in the absence of adequate replacement cells.

In addition to the possibility of gross hemorrhage, which is often observed in specific mammalian species, there is in almost all species the insidious extravasation of red cells out into the tissues, which may occur rather generally throughout the body. A few of these erythrocytes may find their way back into the circulatory channels; however, most of them are entrapped within the tissues and are absorbed by phagocytic cells. Hence, hemosiderin is present in many of the tissues following irradiation and particularly in the reticuloendothelial structures. Large macrophages containing one to several red cells are not uncommonly found throughout the body in the early postirradiation period.

LYMPHATIC

Cytokinetics of Lymphoid Tissue

There are no pathologic changes in whole-body irradiation more intense than the very rapid degeneration and deletion of the small lymphocytes in the various lymphoid structures throughout the body. Under normal circumstances, lymphocytes are present in both blood and lymph circulatory systems and in the lymphoid tissues. These lymphoid structures are to be found in every anatomical area with the major volume located in the spleen and in the various lymph node groups and chains. Smaller amounts are present in the mucosa of the digestive system and in the respiratory tract with additional aggregates identified in other diverse tissues including the bone marrow. Although the morphological characteristics of the small cells of the thymus are similar to those of the small lymphocyte, the behavior of these cells does not entirely conform to that of lymphoid tissue in general and is considered by some investigators to be a separate population histologically and functionally. The lymphoid tissues of the body have one feature in common: the presence under normal circumstances of a large complement of small lymphocytes. The active functional lymphoid tissue may present a varied histologic structure, which is largely, if not wholly, determined by the demands of the body as a whole or by local conditions of stress. Any one lymphoid locus therefore is capable of presenting a variety of histological characteristics depending upon the circumstances at a given time. For example, it may be composed of large numbers of densely packed small lymphocytes so numerous as to all but obliterate the reticular cell framework and the vascular network. In fact, it may contain nodules of even greater cell concentration which may at times have a central germinal center. This germinal center is formed by concentrically oriented reticular cells and encompasses large numbers of medium-sized lymphocytes and some large lymphocytes presenting various degrees of mitotic activity. A highly reactive focus of this type may readily revert to a structure showing a more uniform and less compact distribution of small lymphocytes, or the ratio of small lymphocytes may become diminished with a resultant prominence of the reticular cells along with the fixed macrophages and the free macrophages which are able to respond to the presence of foreign substance. Under certain circumstances the number of these macrophages may be greatly increased by division or by differentiation from primitive reticular cell forms. Other than the afferent and efferent lymphatics and the nutrient capillaries, few endothelial-lined microvascular elements occur as such in these lymphoid structures, although the cords of lymphoid tissue are loosley held by the reticular cells and the fixed macrophages and histologically bear a resemblance to true sinuses.

The principal lymphoid structure of the body is the spleen. Under normal conditions the spleen consists of numerous nodular white pulp areas of lymphocytic activity each with a central arteriole and with the background parenchyma of red pulp. The red pulp is composed of loosely disposed lymphoid tissue arranged in and about sinuses that are, as in the nodes, lined by the fixed histiocytic macrophages. The spleen is a multifunctional unit concerned with lymphopoiesis and possibly antibody formation, a filtration system in the blood stream, an efficient phagocytic organ to clear the stream of cellular debris, and in certain mammalian species an integral part of the hematopoietic system.

The thymus is dissimilar in certain respects from the other lymphoid structures in that it is large and cellular in the embryonic and early postnatal period and then undergoes a progressive atrophy or involution as the individual matures. The cortical zone of the thymic tissue consists primarily of closely packed small lymphocytes, which rarely show any tendency toward development of nodular structures as seen in other lymphoid tissues. The central medullary area has fewer lymphocytes, the reticular-cell pattern being of greater prominence. Many of these reticular cells are epithelioid in appearance, and the characteristic Hassall's bodies of the medulla become more prominent as involution of the gland progresses. Because of its relationship to the early development period of the individual, some hormonal function is assumed to be associated with the thymus in addition to an apparent association with the production of immune response.

In any comprehensive analysis of the response of lymphoid tissue and lymphocytes to the actions of ionizing

radiation, not only must the fixed lymphoid structures of the body be evaluated but the rather large lymphocyte pool that exists in the blood and certain connective tissues of the body must also be considered. The kinetics of this mobile pool are not fully understood, but the pool is obviously in a continual state of fluctuation with lymphocytes cycling in and out by various routes. Extremely adaptable experimental procedures using radioactive labeling have produced evidence in support of certain migratory patterns of the lymphocytes. There is a cycling through the lymph nodes employing both the blood vascular systems and the lymphatics. A similar pattern is employed in the interchange through the thymus with greater emphasis on the direct entry of the lymphocytes into the blood. There is a well-defined afferent transfer of lymphocytes into the spleen and bone marrow, as well as a release from the spleen out into the circulation. As yet, no clear evidence of emigration of lymphocytes out of the marrow exists, but undoubtedly some form of exchange is present. A similar one-way transfer has been identified in the intestinal mucosa, again without a conclusive return.

At least two varieties of lymphocytes are now thought to exist in the body, one having a biological life-span of hours to days and the other surviving for a matter of weeks or months. This large compartment of long-lived small lymphocytes, which appears to be continuously coursing throughout the body, responds to radiation in much the same fashion as those small lymphocytes which are at the time of irradiation in a relatively static condition in a lymphoid aggregate somewhere in the body. It is among these long-lived cells that some investigators have postulated there exist a few that have a greater degree of functional potential than others; that is to say, some of these cells are thought to represent a form of multipotential cell that on migration to the marrow, for example, could undergo cell division with some of the daughter cells establishing pathways of differentiation and becoming hemopoietic precursor elements.

Effect of Radiation on Lymphoid Tissue

Following an acute exposure in the near-lethal to lethal range, the first visible cell alterations will be detectable in less than an hour (Fig. 1.4). The sequence of cytological effects in the lymphocyte begins with the evolution of minute nuclear vacuoles. This is followed by variable condensation and clumping of the nuclear chromatin, which tends to marginate at the nuclear membrane, leaving a pale seemingly empty central area.

The nucleus becomes progressively pyknotic with subsequent cytoplasmic dissolution and nuclear fragmentation. This pattern of lymphocytic degeneration is not specific for radiation and has been observed in conjunction with a variety of cytotoxic and physical agents.

It should be reemphasized that current concepts do not equate the small lymphocyte with the granulocyte or erythrocyte. Although in the small form it is considered nonproliferative, its facility for reversion to the proliferative medium lymphocyte indicates a potential far beyond that of the usual principal parenchymal cell. It is likely that some facet of this inherent characteristic promotes the unusual responsiveness of this cell to radiation.

It should be noted that the lymphocytes of the lymphoid structures are reported to be more responsive to the actions of radiation than the circulating small lymphocyte population. The reason for this apparent variance is not known although it has been postulated that there is some physicochemical alteration in cell composition or a change in sensitivity mediated by environmental factors incumbent on the associated lymphoid tissue.

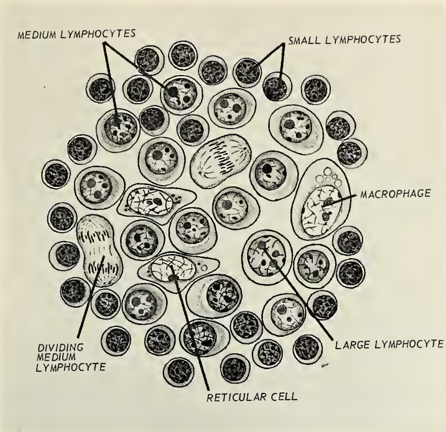
At any given time, including the moment of radiation exposure, there will be a variety of reaction patterns among the innumerable lymphoid aggregates of the body. By implication this means a wide range of lymphocyte density and differing ratios of proliferating lymphocytic cells. Because of this feature plus the heterogeneous quality of most whole-body exposures, there will be all degrees of severity in the acute degenerative response from relatively few damaged cells in the sparsely populated "resting" lymphoid tissues to intense cell destruction in the richly cellular and reactive areas.

The peak of cell destruction and the associated phagocytosis are attained usually within several hours of the radiation event. Thereafter, there is a steady and efficient purging of the cell debris, which is essentially completed within 24 to 48 hr. The total lymphocyte population of the body, both static and circulating, becomes rapidly and dramatically depleted. The now hypocellular lymphoid tissue collapses up on itself and appears as a mesh of relatively empty sinusoids and medullary cords with compact, rounded aggregates of concentrically oriented reticular cells reflecting residua of the reactive germinal centers.

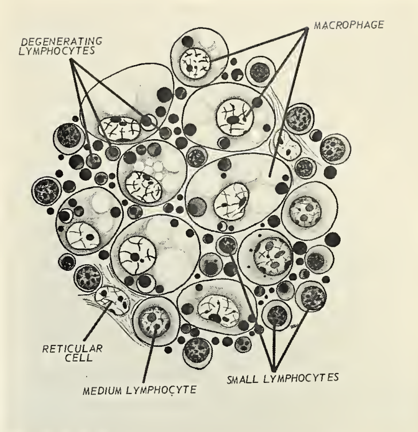
Although this decimation of the lymphoctye population is virtually total with high doses, regenerative efforts become evident during the *2nd* to *4th* weeks after irradiation. The source of this cell renewal is largely conjectural. There are undoubtedly residual lymphocytes either unaffected by the radiation or not sufficiently damaged to prevent their reversion to a proliferative form. There are also presumed to be multipotential primitive cell forms that can be called upon to differentiate along lymphocytic channels. This cell regeneration proceeds with some predilection for perivascular localization in the lymphatic tissues. Later the concentration of lymphocytes, which initially has a high proportion of medium and large cell forms, increases toward the periphery of the node, forms large circumscribed aggregates in the spleen, and concentrates in the cortical zone of the thymus. Germinal centers develop in the nodes and spleen after an additional period of several days.

Irreparable damage to the chromosome structure is responsible for a high proportion of atypical cells. Some of these abnormal lymphocytic cells may be capable of one or more cell divisions, and these progeny may also be distorted, ineffective, and usually short-lived. This will result in a greater than normal ratio of degenerating cells until such time as these mitotically connected cell deaths become diluted down to preexposure attrition levels.

See supplemental Figs. 1.63 through 1.70 for sequential changes in primate lymph nodes.

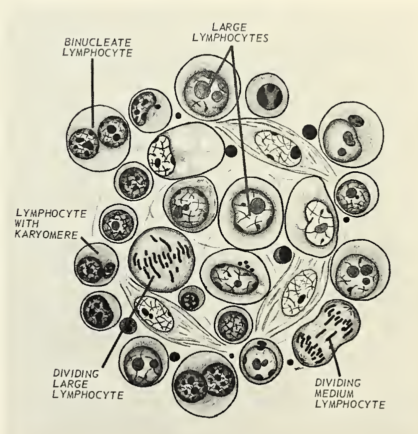


Normal germinal center.



Lymphocyte destruction and phagocytosis.

Depleted nodule.



Regenerative phase.

Fig. 1.4 Lymph nodule.

GASTROINTESTINAL SYSTEM

Cytokinetics of the Gastrointestinal Epithelium

One of the three basic, though arbitrary, categories of radiation death has been identified as the gastrointestinal death. In a way, this is a misnomer or at least misleading in that the primary concern involves the rapid and dramatic response to radiation of the mucosa of the small intestine with a more slowly developing effect observed in the large intestine and an even more poorly defined response in the gastric mucosa. The small intestine is a major component, both anatomically and functionally, of the digestive tract, which begins at the mouth and extends through the oropharynx, esophagus, stomach, small intestine, large intestine, and to the rectum. All the epithelia represented in the digestive tract are of the cell-renewal type, and all are capable of manifesting early severe incapacitative injury as a result of ionizing radiation. In whole-body irradiation, however, it is the mucosa of the small intestine which responds most rapidly and which overshadows the less reactive epithelia in the remainder of the digestive tract. An examination of the relative turnover times of the epithelial populations in the digestive tracts of the rat supports this contention that the small intestine has a more rapid cell-renewal time than any other segment by a factor of 2 to 6.

The cytokinetics of the mucosa of the small intestine evolves along the same basic principles as seen in the hematopoietic tissue. In contrast, however, the epithelium consists of only one cell species, and this is often designated the principal or chief cell of the intestinal mucosa. There is the consideration of the Paneth cells occupying the very base of the intestinal crypts; however, these appear to be of a specialized functional subfamily, although possibly having the same stem cell. Also, in contrast to the bone marrow, this principal cell line does not pass through a series of morphologically distinct subdivisions. Following the final cell division in the zone of proliferation, this immature principal cell undergoes a radical change in its functional propensities with a relatively minor degree of morphologic alteration. Once this cell has passed through the neck of the intestinal gland and becomes an integral part of the epithelium of the villus, it undergoes little or no additional detectable change. It continues to move up the surface of the villus as a mature functional cell and is eventually extruded from the villus tip before any significantly discernible cell senility takes place. The various times associated with the transition from initial cell division to the cell's disappearance from the villus tip have been measured with reasonable accuracy using tritiated thymidine in much the same manner as the kinetics of the hematopoietic cells have been determined.

Radiation Histopathology

A clear distinction must be made between the acute gastrointestinal death as it is associated with whole-body irradiation and those deaths which may follow irradiation of the lower half of the body or the abdomen alone. The term acute gastrointestinal death as applied to death from whole-body irradiation is perhaps satisfactory in a clinical descriptive sense but is inaccurate in its implication insofar as pathogenesis is concerned. When the magnitude of the acute whole-body exposure is such that death occurs in man in approximately 5 to 8 days, the severe injury to the mucosa reaches its maximum at the same time that the pancytopenia, and particularly the granulocytopenia, is also attaining a significantly depressed value. The contribution of this hematologic response to the terminal state must be considered as highly relevant to this form of acute radiation death. It must also be emphasized that the variance in cell renewal and cell transit times among the major divisions of the gastrointestinal tract strongly indicates that the acute denudation of the small intestine precedes any substantial alteration in the mucosae of either the large intestine or the stomach. Consequently, those individuals succumbing to the effects of whole-body irradiation in the range of 1000 to 2500 R do so as a consequence of changes brought about by compromise of the mucosa of the small intestine with the added impact of the lowered resistance largely due to a severe granulocytopenia.

When the radiation involves the lower body or the abdomen only, the hematologic depression is less severe and takes longer to develop. Under these circumstances the degenerative response of the intestinal mucosa is less intense and proceeds more slowly. The opportunity for mucosal regeneration is greater, and metabolite and fluid imbalance are delayed and less severe. Survival in these individuals is expanded.

The progression of the GI syndrome in all mammalian species is characterized by anorexia, abdominal cramping, diarrhea, increasing lethargy, dehydration, and possible evidence of intercurrent infection. Weight loss, diminishing food and water intake, gastric retention, and decreasing intestinal absorption are also present. At the same time, the leucocyte counts fall dramatically to very low values.

The concomitant, progressive electrolyte and fluid imbalance, particularly when associated with severe pancytopenia and deterioration of the biological barrier to potential pathogenic microorganisms, is generally incompatible with life unless intensive supportive measures prove to be effective.

At autopsy, the gross findings may be as follows: the stomach, because of the characteristic postirradiation atony, is often distended with undigested food and liquid; the bowel may be similarly dilated and contain bile-stained fecal material and bloody fluid with a very foul odor; the colon may contain mucus and liquid fecal material, which may or may not be bloody; and mucosal ulcerations may be present, particularly in the small intestine, with some of these deep and even perforating.

As with the hematopoietic syndrome, the gastrointestinal injury in man and primate lag behind those observed in the small-animal species. From the research standpoint, the progressive decrease in total cell population of both crypt and villus is one of the better gauges of the severity of compromise of the intestinal mucosa. An estimate of this cell depression can be obtained by cell counts over a specified area. The corrected weights of carefully sampled bowel segments reportedly reflect the total mucosal cellularity.

The rapid and dramatic histologic response produced in the intestine by ionizing radiation requires detailed consideration (Fig. 1.5). During the first several hours after exposure, a sequence of changes based upon the immediate reaction of the crypt portion of the intestinal epithelium to the radiation evolves. Most of the cells in the proliferative zone will exhibit a progression of morphologic changes reflecting varying degrees of radiation injury. Those which were in relatively sensitive phases of the generative cycle undergo rapid pyknosis and karyorrhexis followed by cell fragmentation. In addition, other cells of this zone will be prevented from entering into mitosis. Many of the remaining cells in this proliferative zone not in the more sensitive phases are also susceptible to radiation and respond by nuclear and cytoplasmic swelling with variable vacuolation. These changes may regress with time or continue to intermitotic death and eventual cytolysis. The amount of cell debris from the initial wave of degeneration reaches a maximum of 6 to 8 hr and then steadily declines through extrusion of this material into the crypt lumen or by phagocytosis.

There is not only an immediate radiation-induced cessation of cell division but a functional suppression of the epithelium, both of which may persist for several hours after the event has occurred. The release of this block sees a full spectrum of damaged cells attempting to complete or enter the generative cycling; hence there is a transient rise in the mitotic index exceeding that of preirradiation values. This remaining segment of the proliferative-zone population may show some prompt cell death as the more severely injured cells attempt to begin division, or there may be inability to accomplish complete cell division with resultant cell death. Some of these cells may be able to complete the division but with production of abnormal daughter cells incapable of normal function or of any extended survival. There may also be other crypt cells that either incurred insignificant damage or had sufficient repair time before entering mitosis so that a normal or near normal division is accomplished. The resultant daughter cells of this group may appear morphologically and functionally normal or may be variably atypical in function and/or configuration. As the magnitude of the dose increases, fewer cells in this proliferative compartment will escape significant injury. Eventually a level will be attained where the recuperative faculty of the crypt epithelium may be altogether nullified, that is, when the stem-cell component has been so severely compromised that it is unable to reconstitute the proliferative zone.

About 24 hr after the exposure, prompt and early cell degeneration directly related to the radiation gives way to progressive cell attrition without cell renewal, which eventually leads to denudation of the mucosa. This second phase begins with a brief latent period. At this time, crypt-cell death is sporadic and near preirradiation levels. There are few, if any, cell divisions, and those which are seen are generally atypical. There is marked depletion of the crypt-cell population with a compensatory shortening of the crypts. The residual crypt cells, with the exception of relatively radioresistant Paneth's cells, are now seen to be pleomorphic and enlarged. Some of these distorted cells begin to appear at the bases of the villi. It should be noted that the mature villus epithelium up to this point remains essentially unaltered, although there is some piling up of senile cells at the extrusion zone at the tip of the villus.

As a result of continued epithelial-cell attrition without renewal, there is a progressive depletion of the overall mucosal epithelium during the subsequent several hours. This impending compromise of the epithelium triggers specific compensatory mechanisms designed to counteract the imminent defect and to perpetuate this biological barrier.

1. There is shortening of the villus and contraction of the crypt which decrease the mucosal surface area.

2. The residual cells, most of which are enlarged and abnormal in configuration, flatten out to cover the greatest possible surface area of the exposed basement membrane.

3. The villus cells are retained beyond the usual functional time span; so they exhibit increasing cytologic evidence of advanced senility. In fact, some may attain this state while still some distance below the villus extrusion zone and prematurely separate from the basement membrane at this point.

4. The stem cells are activated to replenish the principal cells of the epithelium. This is augmented by an apparent shortened generation time among these precursor cells. The efficacy of this event is almost entirely dependent upon the degree of injury sustained by the stem-cell population, and this, in turn, is largely a function of the dose absorbed.

At this point, therefore, the subsequent fate of the epithelial barrier is determined, and, from about day 3 to day 7, further dramatic mucosal alterations occur. When the total dose has been relatively low, the surge of cell regeneration repopulates the mucosa rapidly, replacing the depleted and damaged epithelium. With moderate doses the regeneration will not be as generalized, and there will be numerous crypts so severely injured as to be incapable of evoking a stem-cell response. These crypts will therefore remain atrophic and often cystic. Regenerating epithelium may occasionally dip down into these partially denuded crypts and reline them. If the dose has been very high (1500 to 2500 R and more) foci of regeneration will be spotty and widely separated. The mucosa will become very thin with villi, as such, virtually nonexistent. The basement membrane will be largely denuded, and superficial ulcers will develop. There will be only sparse and distorted epithelial remnants.

The leukocyte count in that dose range which is capable of producing the gastrointestinal syndrome is approaching a severely depressed state in this 3- to 7-day postexposure time period when the greatest degree of intestinal compromise is also evident. It is perhaps fortunate that the other formed elements of the blood, specifically the thrombocytes, are somewhat slower in their decline and as a result do not have a significant bearing upon the nature of the intestinal injury. Hemorrhage in this early acute period is not a major factor, at least in man. The basic defect of the irradiated intestine therefore is the loss of the epithelial lining, which serves as an effective barrier between the luminal content and the circulatory system of the body and acts also in the transport of fluids and metabolites. Excellent experimental investigation has shown that the

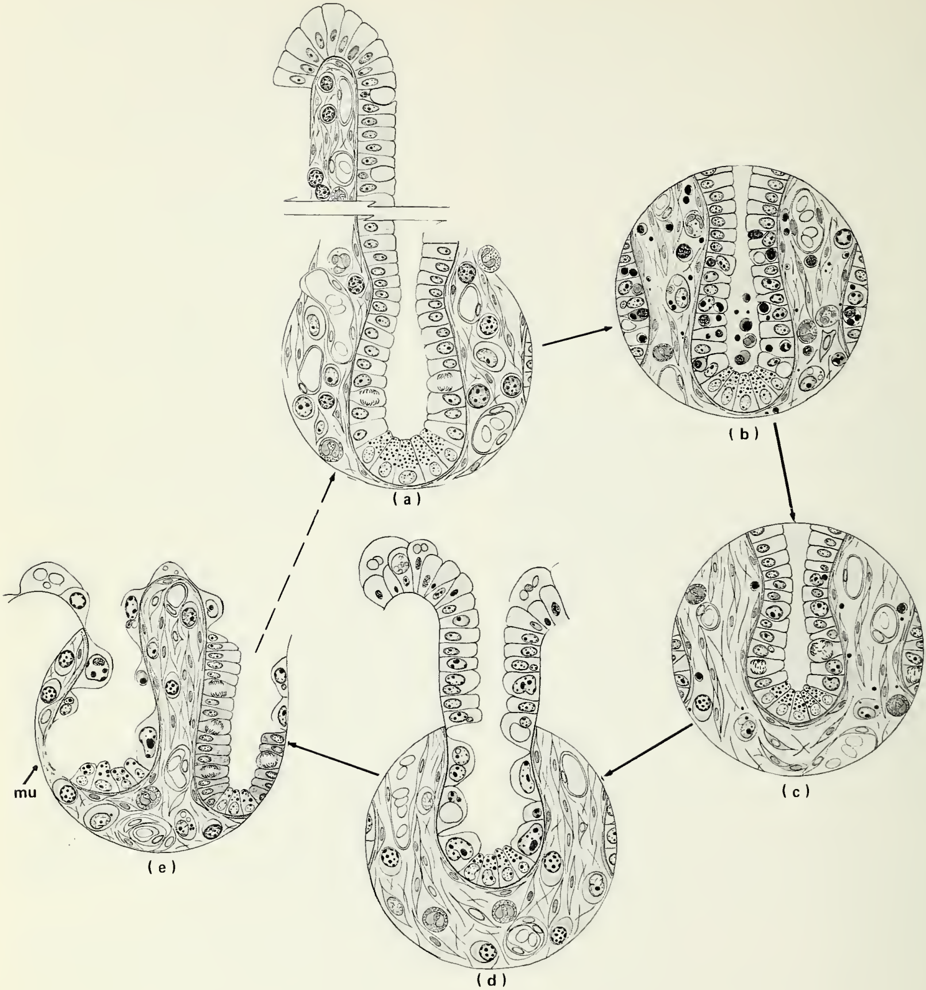


Fig. 1.5 Small intestine. (a) Normal crypt and tip of villus. (b) Peak cell degeneration. (c) Diminished crypt-cell population—early cell atypia. (d) Contracted crypt—foreshortened villus. (e) Mucosal atrophy with microulcer (mu)—focal epithelial regeneration.

probable principal mechanism involved in the gastrointestinal death is severe alteration of the fluid and electrolyte balance.

Relation to Fluid and Electrolyte Imbalance

It is not until the denudation of the mucosa becomes significant and the concomitant diarrhea commences that this severe phase of the fluid and electrolyte imbalance attains prognostic importance.

During the first 2 days no severe illness other than a general lassitude and increased fatigability occurs; and the body electrolytes and the blood volume change very little. For that matter, some animals have been shown to exhibit an increased fluid intake during this period of time, and their urinary output is similarly increased. Following this initial brief latent period, however, the exposed individuals become progressively debilitated with a reduction of fluid intake. Although vomiting may be a part of the syndrome, the amount of fluid and electrolytes lost in this manner during the relatively abrupt course of the illness is of little clinical significance.

During the terminal phase of this gastrointestinal syndrome (days 3 to 5), the rapidly progressive denudation of the intestinal mucosa induces severe diarrhea, which may be blood tinged. Experimental evidence has indicated the probable role of bile in the aggravation of this terminal diarrhea. The bile salts, which are ordinarily reabsorbed through the distal ileum, are retained in the lumen. The presence of this increased concentration of bile in the small intestine and colon additionally provokes the diarrhea. Diversion of the bile away from the gut lumen or ligation of the bile duct is effective in substantially decreasing the diarrheal response in heavily irradiated animals.

This severe outpouring of fluids and electrolytes produces a rapidly progressive dehydration and diminished blood volume, much in excess of that which might be expected from decreased intake alone. At the same time, loss of electrolytes, specifically sodium, reflects the failure of absorption or resorption as a result of the denuded or defective epithelium.

The absorption of nutrients through the intestinal wall is also obviously impaired as a result of the severe mucosal damage; however, this effect is of little clinical consequence in whole-body irradiation of this magnitude because of the anticipated abbreviated survival time. If the duration of life is prolonged beyond several days, then this condition may introduce a severe nutritional deficit and become a major therapeutic consideration.

Similar Histopathology in Therapeutic Irradiation

It is of interest to compare the acute changes observed in whole-body irradiation with those associated with an intermittent type of exposure. Trier et al. performed peroral biopsies serially from selected patients before, during, and after the administration of 2000 to 3300 R of X-ray therapy to the abdomen given in fractionated doses of 150 to 300 R, 5 or 6 days per week. After the radiation exposure began, the villi showed a progressive shortening with a resultant decrease in the overall depth of the mucosa. There was a concomitant increase in the concentration of cells in the lamina propria, first, by a compaction of the laminar cells resulting from the shortening of the villi and, second, by an infiltration of lymphocytes, which, during the course of the therapy, diminished and were replaced by a proportionate increase in plasma cells and in some instances a significant number of granulocytes. Depression in mitotic activity became obvious within 12 hr after the onset of irradiation and then continued throughout the irradiation program. In the crypts the total population became diminished, and the cells were inordinately large with frequent multinucleation. Discrete spherical bodies were present within the cytoplasm of many of the crypt cells, which contained Feulgen positive materials. Similar structures have been described in the crypt cells of man after exposure to some of the so-called radiomimetic drugs.

With this type of intermittent localized irradiation, after several days, changes were also observed in the villus cells. These cells were shorter and broader than those before irradiation; the nuclei were somewhat larger, and binucleate cells were not uncommon. "Crypt abscesses" formed; these are not really abscesses in the accepted sense of the word but are pseudocysts formed apparently by constriction of damaged crypt areas lined by distorted epithelial cells and containing cellular debris and possibly some inflammatory cells. Indeed, some of these isolated foci may subsequently become true microabscesses. These investigators also performed serial biopsies from the mucosa distant from the area of irradiation and found no alterations in the mucosal morphology as compared to the pretreatment epithelium. This seems to indicate that at least, when a limited portion of the intestine is exposed, the portion not included within the field of radiation retains a normal histological appearance and presumably a normal functional capacity. There continued to be some contention with regard to the exact nature of the spherical bodies seen in large numbers within hours after irradiation, and it may be quite possible that there is no single etiology. Most investigators contend that these bodies represent degenerative materials from either the cell in which they are found or from disrupted contiguous cells of the proliferative zone in the crypt. There is also evidence that some of this debris stems from the destruction of lymphocytes in the lamina propria.

Relation to Microcirculation

Although by far the greatest degree of emphasis with regard to the response of the intestinal tract to radiation rests on the effects observed in the epithelial lining, several other very important components make up the intestinal mucosa. It is generally accepted that the small vessels of the body are relatively responsive to radiation and that certain changes which may or may not be entirely reversible can be observed within the first few days after the radiation event. As more investigators become interested in the response to radiation of the microcirculatory apparatus of specific organs or tissues, it becomes apparent that, indeed, this effect may be an important factor in the development of

early lesions involving the principal cell components of that tissue and in the capacity for repair or recuperation of that tissue. The reasons for this increased emphasis are rather obvious. First, the principal cell components of the tissue are dependent on this microvascular network for proper life support, and, second, the endothelium of these small vessels exhibits a greater degree of responsiveness to radiation than was originally thought. These vessels respond by endothelial swelling, by an as yet unexplained endothelial cell concentration, by increased permeability of the endothelial barrier, and by variable degrees of swelling and vacuolation in the associated smooth-muscle cells of the vessel wall. All these changes will lead to some degree of constriction of the vessel lumen, the probability of focal tissue ischemia, and the possibility of development of occlusion by thrombosis. Studies by Eddy and Cassarrett employing microangioradiographic procedures supported by histopathologic examination reveal these microvascular changes to be spotty in development along the course of a vessel and, in the intestinal mucosa, to be accompanied by variable degrees of increased vascular tortuosity. With the passage of time, the early changes either undergo some degree of reversal or form the basis for more permanent change, such as enlarged and atypical endothelial cells; clusters of endothelial cells; presence in the subintimal areas of a dense hyalin-like material; and progressive degenerative changes in the media, such as diminished nucleation, a hyalin-fibrinoid alteration, and occasionally necrosis. The microangioradiograph of the irradiated intestinal mucosa tends to confirm impressions gained by examinations of serial tissue sections. There is a shortening of the villi subsequent to irradiation, and this is reflected in a shortened path of the mucosal vessels and an increase in their tortuosity. In addition, the number of these smaller vessels appears to decline, and at times, there are focal areas where the vascular depletion is even more pronounced. In contrast to the many foci of constriction, there is also apparent dilation of some of the vessels, which is a radiographic reflection of the ectasia which is often identified on histologic preparations.

Eddy and Casarrett have also shown that, although the relatively large circumferential arteries of the mucosa and submucosa reveal little or no alteration of their patency, the submucosal arterioles whose branches supply the crypts and villi are the vessels that show the greatest amount of focal obstruction and interference with normal flow. As the investigations of the microcirculatory system of the intestinal mucosa in particular and the entire body in general become more sophisticated and more complete, it is probable that there will develop a direct relationship between the extent of circulatory obstruction to a specific population of principal functional cells and the magnitude of the resultant degenerative change that has become a recognized part of the overall concept of whole-body radiation injury. In some respects this relationship may not strictly hold true for the epithelial cells of the intestine in that these particular cells are apparently privileged to obtain some nutritive materials directly from the content of the bowel lumen and are therefore not totally dependent on the microcirculatory system for their supplies. This will of course not be the case in other organs of the body.

Relation to Other Mammalian Studies

Analyses of various types of experimental animals have produced interesting observations on certain aspects of the intestinal response to irradiation. There is considerable experimental evidence to support the contention that there is actually a detectable increase in survival time in some species of irradiated hibernating animals, whereas other observers feel that once the nonhibernating state is resumed, the irradiated animals then go on to develop the radiation response just as they would under normal circumstances. There are, however, two reasons to feel that irradiation of hibernating animals may produce an extended survival time: (1) there is diminished demand for cell renewal; therefore, cell proliferation in these systems is at a minimum, and (2) the markedly depressed metabolic and functional complex allows for a much greater time interval in which to completely or partially repair molecular and organelle damage that, in a nonhibernating animal, might produce prompt cell death or irreversible injury.

There is still a certain amount of controversy regarding the differences in lethality between conventional mice and germ-free mice subsequent to total-body irradiation. The assumption is most often made that the presence of microorganisms in the intestinal tract is the basis for a terminal state of bacteremia or toxemia. This condition is brought about by the compromise of the biological barriers affected by the intestinal mucosa and is further enhanced by the general depression of other body defense mechanisms, such as the hematopoietic components and the immunologic capabilities. As to the differences between germ-free and conventional animals, it can only be assumed that in both there are similar histopathologic changes with the superimposition of microorganismal invasion accelerating the demise of the conventional animal.

It is logical to conclude that doses of radiation in the range consistent with gastrointestinal death will produce an overall debilitation of the life processes which is highly conducive to the development of both local and systemic infection. Among the many individual defects that contribute to this state are the following: severe pancyotopenia but more specifically a granulocytopenia, a severely compromised gastrointestinal barrier, a profound decrement in the fluid and electrolyte balance, weight loss and deficient nutritional reserve, and a depopulation of the lymphoid foci throughout the body, specifically those associated with the gastrointestinal tract. That each of these factors plays a significant role in the development and progress of the gastrointestinal syndrome has been shown by a variety of experimental exposures on several mammalian species, e.g., the selective shielding of portions of the intestine, protection of the marrow or spleen from the radiation, the application of antibiotics subsequent to the irradiation, and the employment of germ-free or gnotobiotic animals. Any degree of protection of either the hematopoietic system or a segment of the intestinal tract may extend the survival time of the irradiated individuals.

It has been assumed, whether correctly or not, that with irradiation of the abdominal region alone the number of circulating granulocytes should decline substantially because of the inclusion of the spleen and areas of marrow

within the radiation field; consequently, the larger the area of abdomen involved in the radiation, the greater the degree of granulocyte depletion. However, there have been no definitive studies in this regard, and this is worthy of some evaluation if one is to consider that the granulocytopenia plays a significant role in the development of the intestinal syndrome. It has been considered probable also that there is a direct relationship between the degree of granulocytopenia and the rapidity of loss of the epithelium. Some evidence for this is seen in the radiation of germ-free animals where the lack of bacterial flora within the intestine seems to delay the loss of the epithelial cells.

Radiation in moderate doses tends to reduce the motility of the intestinal tract, and this, in turn, acts to alter the ratios of the luminal flora. It has been shown that the numbers of enterococci and coliform bacilli will increase disproportionately at the expense of other bacterial species that are required for the proper accomplishment of certain digestive processes. This same condition results in an expanding pool of potential pathogenic organisms and endotoxins, which may penetrate the mucosal barrier as the epithelium becomes compromised.

TESTIS

Cytokinetics of Spermatogenesis

The testis is an encapsulated glandular structure consisting predominantly of convoluted seminiferous tubules that are lined by germinative epithelium palisaded upon a supporting basement membrane. The interstitial tissues consist of collagen fibers, fibroblasts, and the interstitial Leydig cells along with the small nutrient blood vessels, lymphatics, and nerve bundles. As in the other tissues of the body that show dramatic changes subsequent to irradiation, the epithelium of the seminiferous tubules is of a moderately rapid cell-renewal type, the progression of cell maturation proceeding from the basement membrane inward to the lumen of the tubule. The more primitive spermatogonia with interspersed Sertoli cells are situated in close apposition to the basement membrane. The earliest progenitor cells are the type-A spermatogonia, which divide mitotically reproducing themselves and also producing daughter cells of a slightly more differentiated or mature form designated the type-B spermatogonia. There are apparently two populations of type-A spermatogonia, one being a short-lived cell with a short intermitotic interval. This component appears to be a radiosensitive cell. The other component is a long-lived type-A cell with a long intermitotic phase. This latter cell type is much less responsive to radiation and is considered by some investigators to be the precursor cell of the seminiferous tubule epithelium. It is possible, however, that there is an even more primitive and undifferentiated cell (stem cell) situated along the basement membrane, which, under certain circumstances, may be activated and produce the type-A spermatogonia. The type-B spermatogonia progress through a series of mitotic divisions with eventual maturation to primary spermatocytes. At this point, further division is of the meiotic type and results ultimately in spermatids containing a haploid complement of chromosomes. The smaller secondary spermatocytes further divide to produce even smaller daughter spermatids. These spermatids come to lie within indentations of the luminal surfaces of the Sertoli cells from whence they apparently derive critical nutritive substances. In this last phase of spermatogenesis, a remarkable structural and functional transformation occurs which culminates in the evolution of the mature sperm. Once loosed from the bonds of the Sertoli cells, the sperm lies free in the lumen and is eventually expelled or undergoes cytolysis.

This vertically polarized cell-renewal process, which ultimately produces mature sperm, is not a uniform process along the length of the seminiferous tubule but occurs in a periodic or linear wavelike progression. The transit time from the first appearance of the type-A spermatogonia to the extrusion of the mature sperm into the lumen of the seminiferous tubule has been indicated as being approximately 64 days in the human. This extended time interval is one reason for the slow diminution of the sperm population under circumstances of developmental arrest. A multitude of situations may produce degeneration and atrophy of the spermatogenic epithelium, such as unusual conditions of cold or heat, trauma and inflammation, a variety of infectious disease processes, and dietary discrepancies. In each of these the normal spermatogenic activity is usually restored fully or partially once the stress has been removed.

The Effects of Radiation on the Testis

The compromise of the cell-renewal system of the seminiferous epithelium by ionizing radiation is based upon the relative sensitivity of the spermatogonia with prompt destruction of those spermatogonia which are in a sensitive phase of their generative cycles at the time of the exposure; delayed degeneration among those spermatogonia which, though injured, may go on to attempt cell division and die in the process; and those progeny of injured spermatogonia which are incapable of further division or which eventually succumb to the radiation-induced cellular defects (Fig. 1.6). Similar mitosis-connected cellular abnormalities and cell deaths may be associated with the type-B spermatogonia as well as with the type-A. Those more mature and differentiated cells known as the spermatocytes are somewhat more resistant to the moderate doses of radiation which severely affect the more primitive spermatogonia. However, such damage may be incurred as to preclude any normal meiotic division and further differentiation into mature sperm. In general, some comparisons can be made between the progression of the cell renewal system in the seminiferous tubule and that observed in the intestinal epithelium. The primary compromise is based upon a deficiency in the production of principal cells followed by a progressive depopulation of the epithelium.

There is a latent period before the injury induced by the radiation is alleviated and the proliferative cell component is reactivated, as in the crypt of the intestinal epithelium. The duration of this latent period is several weeks to months, however, as compared to the 8 to 12 hr block observed in the crypt epithelium. The extent of this delay is largely dependent upon whether the vast majority of the type-A spermatogonia have been depleted. Ulti-

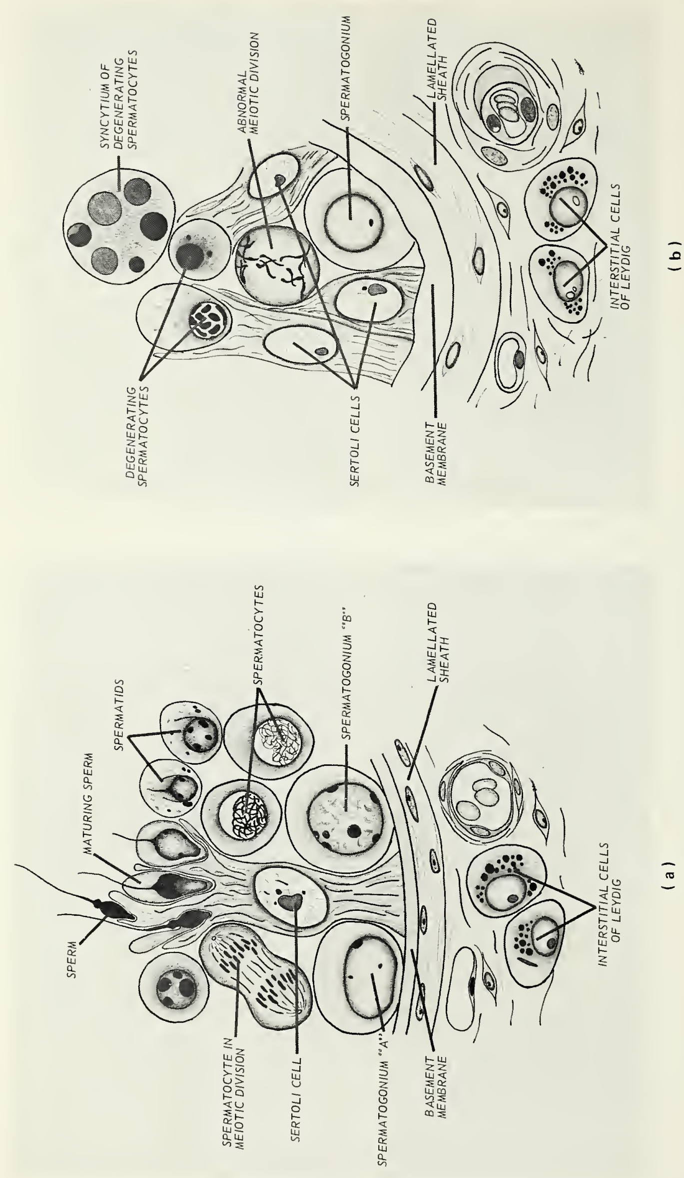


Fig. 1.6 Testis. (a) Normal tubule segment. (b) Compromised spermatogenesis.

mately, a basic stem cell, possibly an undifferentiated cell associated with the basement membrane, must be called upon to reinstitute spermatogenic activity. There is no proof of this process although evidence speaks in favor of the existence of such a mechanism. Although the time factors of the kinetics of spermatogenesis in the human have not been accurately determined, the sequential changes that occur and the defects induced by irradiation of this generative epithelium are reasonably well defined. The stress of ionizing irradiation on the testes produces an immediate depletion of those spermatogonia in a sensitive phase of their reproductive cycle. A second wave of cell destruction is associated with those damaged cells which attempt to enter or complete mitoses but which have been rendered incapable of accomplishing this process and another component of spermatogenic cells which has received injury allowing completion of one or more mitoses but whose progeny may be incapable of division or of continuing maturation. A fourth segment of the spermatogenic cell population comprises those cells which have incurred sublethal structural injuries and chromosomal damage but which are capable of continuing the maturation and developmental process and eventually enter the lumen of the seminiferous tubules as mature sperm and are expelled in a normal fashion. Those sperm which were mature at the time of exposure are resistant to radiation and these will not carry any chromosome defect.

In the early postirradiation period during which the sperm population in the seminiferous seminal fluid is still sufficient to maintain fertility, normal sperm are mixed with more recently matured sperm that may carry a genetic defect. This underlines the danger of conception in this first postirradiation phase. As the period of extreme hypospermia or aspermia is reached, sterility occurs in the irradiated individual which has a variable degree of permanency. If spermatogenesis becomes reestablished and attains a sufficient proportion to achieve fertility, the possibility of transmission of genetically linked abnormalities to the conceptus is much less likely, presumably because these sperm are the product of stress-activated primitive or stem cells and, as such, will not be transmitting any radiation-induced chromosomal defect. A patient reported by Hempelmann, Lisco, and Hoffman (1952) and Oakes and Lushbaugh, (1952) was studied by means of serial seminal fluid examinations and also testicular biopsies over a period of 5 years following an accidental whole-body exposure to mixed gamma and neutron radiation. Their results indicated the depletion of the sperm count to occur over a period of several months to eventually reach essentially an aspermic condition. Although the exact timing was not very critical, biopsy evidence showed renewed spermatogenic activity at 20 months, which slowly progressed to a condition compatible with fertility at approximately 50 months. It must be assumed that these values may vary broadly depending upon the nature of the radiation received, including the total dose and the time over which the radiation is given.

Although irradiation of the testes probably has no effect upon the physical well-being of the individual, nevertheless irradiation even in subclinical quantities will produce variable degrees of sterility. The early response of the testicular tissue is highly selective in nature in that the germinal epithelium of the seminiferous tubules responds with relative rapidity to the radiation. Effects upon the vascular and ductal structures are less obvious and more protracted, and the interstitial cells of Leydig are considered resistant to the action of radiation. As a consequence, doses of radiation which are adequate to produce degeneration and subsequent atrophy of the seminiferous tubules will have no appreciable effect upon the hormone-producing capacity of the interstitial cells and, therefore, will result in no subjective or objective change in the individual physical characteristics other than a decrease in the size of the testes and a softening of their consistency.

This lack of symptomatology referable to the irradiated testes requires that any clinical evaluation of the degree of damage be based upon sequential analyses of the seminal fluid. In general, the volume of ejaculate will be little, if at all, diminished although it may become progressively more watery as opposed to the usual viscid consistency. The concentration of the sperm within the fluid is of great significance and shows onset of oligospermia within a few months at moderate doses. The decrease in sperm population continues over a period of several months.

Under normal conditions the count ranges well over a million per milliliter, and, once this level drops below 20,000 per milliliter, fertility is very severely impaired. In addition to the depression in sperm count, there may be dramatic alterations in the number of sperm that have a normal degree of motility and an increasing ratio of sperm that are abnormal both morphologically and functionally. There is no danger to the irradiated individual insofar as this injury to the testicular tissue is concerned. However, because of the genetic injuries produced by the action of radiation, steps should be taken to avoid at all costs the production of progeny during this initial phase of progressive testicular injury. During this time there would be an increased probability for the production of embryonic abnormalities, which increases the ratio of abortions, stillbirths, and abnormal viable offspring.

CENTRAL NERVOUS SYSTEM

Cytokinetics of the Central Nervous System

The diversity of the histological composition of the central nervous system is exceeded only by the complexity of its functional attributes. The relative inaccessibility of the central nervous system parenchyma and the difficulty of developing highly sophisticated means of determining early functional changes and morphologic alterations make analysis of response to radiation extremely difficult. From the cellular kinetics aspect, the primary parenchymal cells of the mature central nervous system are in a nonproliferative steady state—all cell division, differentiation, and maturation of the neurogenic elements occurs in the embryo and neonatal period with no further significant proliferation throughout the life-span of the individual. Even under conditions of extreme challenge or stress, the neurons do not revert to a proliferative state, and there is no recognized activation of a stem-cell component. For that matter, a very minute but steady attrition of functional neurons occurs throughout the life of the individual with

no replacement of these destroyed cells. It is interesting to note, therefore, that under the stress of radiation, it is not the actual physical loss of the mature functional cell which results in the early compromise of the body as a whole, such as is seen in the pancytopenia induced in the hematopoietic tissue or in the denudation of the intestinal mucosa, but is in contrast a defect in the functional constitution of the neuron. Furthermore, the lethal effect of extremely high doses may be in part a sequela of direct changes occurring within the neurons, whereas the deaths resulting from either gastrointestinal or hematopoietic compromise are predominantly indirect in nature. In other words, the physical loss of these latter cells produces decrements in overall body processes which are incompatible with life.

The principal cell of the central nervous system is the neuron, which consists of the large cell body, numerous short dendritic processes, and a single axon that may vary greatly in length. Abundant neuroglial cells provide the supporting matrix and mediate the metabolic requirements of these primary functional cells. These neuroglial cells have been subclassified into the macroglial cells—the astrocytes and oligodendrocytes—which are of ectodermal origin, as are the neurons, and the microglial cells, which stem from mesodermal elements that were carried into the parenchyma by the penetrating vascular channels. Also categorized with the neuroglia are the epithelioid cells of the ependyma seen in the choroid plexus and lining the ventricles. The substance of the brain and spinal cord is encased in the meninges, which is a composite of three membranes, the relatively tough outer dura mater, the thin arachnoid, and the richly vascular pia mater, which is closely adherent to the underlying parenchyma.

The major blood supply to the brain is via the carotid arteries and the large vessels which conjoin at the circle of Willis. From these primary conduits extend innumerable ramifications coursing through the pia mater and deep into the parenchyma. There are no lymphatic vessels within the brain and spinal cord. A great deal of discussion has centered about the so-called blood–brain barrier both as to its anatomical location and its method of action. Because the primary functional elements of the central nervous system are highly susceptible to a variety of circulating chemical and biological substances, a blocking mechanism retards the transmittal of such agents. This barrier is generally thought to be associated with either the endothelial–subendothelial complex within the vessels or the coalescence of the bases of the neuroglial processes as they impinge upon the outer surface of the vessels. The contention that the primary parenchymal elements of the central nervous system are relatively unresponsive except to very high doses of radiation leads many investigators to consider with much greater criticality the potential compromise of the blood–brain barrier and its secondary impact upon the functional state of the neurons through alteration of the microenvironment.

The Central Nervous System Syndrome

The CNS death is primarily a critical response to some drastically altered physiologic process that is incompatible with life, and it occurs with such rapidity that there is little visible manifestation, at least by the means presently available for such analysis. When the whole body is subjected to excessively high doses of penetrating radiation, a stormy and fulminating clinical course ensues, terminating usually within 24 to 48 hr. The clinical manifestations that mark the course are characteristic of central nervous system irritation or injury. There is no set pattern although agitation may be the first recognizable symptom, and this may be followed very shortly by confusion, disorientation, ataxia, and disturbances in equilibrium. Other clinical features that may also be referable to the central nervous syndrome are vomiting, progressive apathy, and prostration; convulsions followed by coma; and then death. Depending upon the dose received and the duration of survival, there may or may not be a very limited latent period during which the individual may seem relatively normal, although poorly responsive.

The term central nervous sytem syndrome should not be taken too literally. Certain concomitant symptoms, such as vomiting, uncontrollable watery diarrhea, variable abdominal cramping, prostration, hypotension, and shock, could have as their basis the overwhelming and widespread prompt cellular destruction and functional arrest throughout many tissues of the body induced by the inordinately large quantity of radiation. It is known, however, from careful investigations of head-only irradiations of several mammalian species that acute deaths can be produced with symptomatology similar in many respects to that described for the central nervous system syndrome of whole-body irradiation.

It has not yet been satisfactorily determined whether these defects result from direct action on the composition and function of the principal cells or reflect the toxic effects of substances released in the ground substance by transudation through an altered vascular barrier exhibiting no visible defect or through primary chemical decomposition in the impulse-transmittal system. It must be conceded, however, that the so-called central nervous system syndrome or central nervous system death as a category of whole-body irradiation is largely based upon clinical observations and symptomatology with definition of functional deficits still in a relatively unsophisticated status.

Because of the extreme rapidity of the progression of the central nervous system death, categorization of the clinical response in relation to total dose involves use of extremely large doses of pulsed radiation. There is, in fact, little practical value to such evaluation.

A dose of 200,000 R generally produces prompt convulsive events and death within a matter of a few minutes. The implication, of course, is that critical functions within the nerve cells or at the all-important synapses are immediately disrupted.

A dose of 20,000 R results in the very rapid development of convulsive episodes, ataxia, loss of coordination, coma, and death in minutes to hours.

The general symptomatology and clinical signs are largely referable to the central nervous system, and, although morphological changes are minimal, the implication is that the primary defect is again localized to the principal parenchymal cells of the brain. Survival time in

excess of 30 min, however, allows for tremendous cellular destruction in the sensitive tissues throughout the body, and the role of this overkill in the early demise of these individuals has not been fully evaluated.

As the radiation dose is further diminished, the possible role of the central nervous system in the ultimate outcome of the overall injury is considered relatively insignificant. In those individuals exposed to several thousand rads, the initial symptomatology may be similar in many respects to that observed with the so-called central nervous system death, such as confusion, delirium, lack of coordination, ataxia, aphasia, and perhaps even convulsive seizures. This prodromal symptomatology is generally of short duration and is accompanied by vomiting and diarrhea. It is succeeded by a latent period of variable duration which gives way to the overt manifestation of the whole-body irradiation syndrome, now referable to the gastrointestinal and hematopoietic systems.

Below the dose range at which central nervous system symptomatology occurs, sophisticated telemetering devices may indicate fleeting alterations in the usually steady activity of the central nervous system elements. These deficits probably play little or no part in the prognosis of the exposed individual. It is possible, however, that with the dose range above 1000 R, any such minute lesions within the brain may contribute to irritability or apprehension.

The recuperative powers of most of the cell-renewal systems of the body are rather astounding, and in many instances the reformation is complete and the functional integrity is entirely restored. Complete recovery does not always occur, and it is not the case in every tissue. For example, the testes are prone to develop some degree of permanent atrophy and sterility. Epilation may be permanent, and even the mucosa of the small intestine may not recover its full absorptive potential. By this same token, then, it is of some academic interest to consider the possibility of some degree of decrement in the functional capacity of the central nervous system, even though the original amount of radiation was insufficient to produce prompt measurable clinical symptomatology. Information of this type would of course be most applicable in those instances where the dose to the head was relatively high but there was sufficient sparing of the other body structures to permit extended survival. Experimental studies have disclosed that irradiation of the developing brain, for example in in utero exposure, does alter the later capacity of the individual to perform certain functions and does produce deficiencies in coordination and sometimes emotional instability. Whether this is due to a depletion of the normal complement of neuronal elements or whether it is a functional defect in the existing neuronal elements is not fully understood.

The relative responsiveness of vascular components may lead one to the unsupported implication that the primary basis for the central nervous system response is in some way related to circulatory embarrassment or the perfusion of some toxic substance through the brain parenchyma. It should be realized, however, that there are undoubtedly disruptive effects at the molecular and macromolecular level of the neuronal elements which by present methods of analysis cannot be adequately evaluated. Given enough time following an exposure in the multiple kilorad range, these physical–chemical alterations would become biologically amplified and eventually would be manifest as morphologically identifiable or functionally detectable lesions.

Assuming the absorption of very large doses of radiation, there remains a great deal of controversy as to exactly where in the complex makeup of the central nervous system this ionizing radiation exerts its greatest effect. With regard to the afferent impulses that feed stimuli to the brain, certain forms of the sensory receptors might be activated by intense ionization in much the same manner they are by such agents as heat, cold, vibration, etc., and send an impulse to the brain. It is possible that this signal could take the form of a visual sensation, a tactile sensation, or perhaps even an auditory response.

The basic functional element of the central nervous system is the neuron. Within the highly complex composition of this cell is the capacity to receive stimuli, to act upon the stimuli in some fashion, and then to generate a response. The complexity of this function alone would dictate that this should be the focus of greatest sensitivity to ionizing radiation; and, although the neuron itself might retain the physical properties of a living cell, the action of the radiation could result in many diverse alterations within the functional makeup of the neuron. With regard to the transmission of stimuli to the neuron and impulses away from this parenchymal cell, the processes at the synapses apparently are relatively radioresistant and require considerable irradiation to produce block. Experimental evidence indicates that the various portions of the brain exhibit different degrees of responsiveness to ionizing radiation. Arnold et al. (1954) pointed out that damage to the brain stem and also to the hypothalamus occurred at doses of 1800 R, which by his determination was approximately one-half that required to produce similar changes in the cerebral cortex. Clemente and Holst (1954) also identified injury in the hypothalamus and the medullary regions in the dose range between 2000 and 3000 R. In addition to the increased susceptibility of the parenchymal cells of these areas to degeneration, they also pointed out apparent compromise of the blood–brain barrier, which is more prominent in these sites than in the cerebral cortex.

One of the early visible changes reported in the nerve parenchyma may appear in 2 to 3 weeks following a very concentrated exposure to ionizing irradiation. It consists of focal, irregular, and randomly distributed patches of myelin degeneration. In association with this the nerve fibers may or may not be fragmented themselves. There is particular disagreement with regard to the response of the glial cells to ionizing radiation, with some investigators indicating early swelling of these cells followed by pyknosis and cytolysis. These effects are reported to appear 4 to 6 weeks following high doses of ionizing radiation and eventually result in a zone of relative acellularity within the brain parenchyma which may progress to necrosis. Other investigators using similar dose ranges have indicated that the response of the glial cells is insignificant even at these relatively high doses. Because there is a great diversity in methods of investigation including the use of radically different species of animals and multiple types of radiation and modes of

delivery, some of the disagreement as to the nature of the radiation responses is understandable and is to be anticipated. A great deal of additional experimental work will be required before these variations can be satisfactorily identified and correlated. As has been found true with all other parameters of radiation response, there is considerable individual susceptibility to the actions of ionizing radiation.

The puzzling response of the granule cells of the cerebellum is also an early manifestation of radiation effect. Experimental studies by Haymaker, Vogel, and Wilson (in Haley and Snider, 1962) concerning the pyknotic change in the granule cells of the cerebellum all confirmed the impression that this was largely a transitory and reversible response. Much of this experimentation was carried out in primate species, but similar changes have been found in rabbits, guinea pigs, and small rodents.

It is perhaps pertinent to examine in greater detail the reaction that occurs in the granule cells of the cerebellum following a high dose of radiation. The primary effect is a reduction in the nucleus to half the usual size. The cytoplasm, normally obscured by the relatively large nuclear–cytoplasmic ratio, is easily differentiated about the shrunken nucleus. There is no predilection insofar as a site for this response, and those granular cells which do react are distributed at random throughout the cerebellar fronds. Those affected cells that are destined to continue to degenerate rather than revert to normal do not appear to provoke any significant degree of phagocytic response or leukocytic infiltration.

To explain the transient and reversible nature of this response in the relatively lower doses, Vogel has suggested that a transfer of substance from the nuclei into the cytoplasm, either actively or passively, through a nuclear membrane that has suffered alteration in its permeability.

Investigations in which unusually intense doses of radiation were administered locally to various portions of the brain disclosed distinct and rather rapidly progressive degenerative changes in the neurons and neuroglia. Because these changes occurred before the microcirculatory apparatus was significantly altered, it was concluded that the effect was a primary one upon the nerve-cell components and their processes. To confirm this, investigations of the patency of the capillary bed were conducted during the period of development of the necrosis, and no significant reduction was found in the capacity of this circulatory system (in Haley and Snider, 1962). With continued passage of time, postexposure injury to the vessel walls has been found not only within the primary area of radiation-induced necrosis but also at considerable distances from this area of severest injury indicating a greater degree of vessel responsiveness to smaller doses of radiation in the peripheral areas where there is dose attenuation. A review of case reports and experimental investigations in the field of irradiation of the central nervous system discloses certain very early appearing lesions that occur in the absence of visible nerve-cell injury and with enough consistency to be considered characteristics of radiation response in the brain and spinal cord. One of the earliest effects to be detected is one that is not unique to the nervous system but is identified in all irradiated tissues, and that is the changes brought about in the vasculature and, more specifically, in the microcirculatory system. There seems to be general agreement that the earliest alterations observed are swelling of the endothelial cells with a less pronounced response of similar nature in the encircling smooth-muscle cells. This change may be of a temporary nature with subsequent complete reversion to a normal appearance. During this period of damage, however, definite indications of defects of the endothelial barrier are present with extrusion of fluid, leukocytes, and erythrocytes into the perivascular zone. Although the initial leukocyte exudate is primarily granulocytes, these are replaced, with the passage of time, by monocytes and macrophages containing hemosiderin granules. These leukocytic infiltrations within the brain proper remain localized and show no predilection for extension deeper into the substance of the brain. In contrast, that infiltrate which occurs about the vessels in the meninges, although initially localized, tends to spread throughout the membranes over the gyri and down deep into the sulci. The response in the choroid plexus is similar.

If bacteria can be ruled out as the etiologic agent, there are two other principal considerations: (1) tissue damage resulting from irradiation (however, this is not sustained by morphologic studies in the early postirradiation period) and (2) the presence of reactive substances within the tissues which are produced by the action of the radiation and are not properly dissipated, again by virtue of the radiation.

Large hemorrhages are rarely encountered in this very early postirradiation period. Because of the abnormally increased diffusability across the vascular walls, some perivascular edema may be present which may contribute to an early acute overall swelling of the brain substance. As the time following exposure increases, some of the damage may progress and become permanent with disruption and fenestration of the larger vessel walls, which become infiltrated first by granulocytes and then by mononuclear leukocytes. A true necrotic vasculitis may eventually develop with an associated vascular occlusion by thrombosis. Further progression of the vascular lesions to enlarged and tortuous vessels with markedly thickened and hyalinized walls and markedly constricted lumens is a delayed effect not pertinent to the acute total-body irradiation picture and will not be considered in any further detail.

The relative importance of the blood–brain barrier has been emphasized by Clemente and Richardson (in Haley and Snider, 1962). They indicate that because it has been shown that a vascular and perivascular inflammatory response and edema follow irradiation of the brain and because the neurons are known to be very sensitive to chemical alterations of their immediate environment, it should be reasonable to assume that any defect or compromise of the so-called blood–brain barrier might be responsible for secondary detrimental changes in the functional nerve cells. There have been many experimental studies to indicate that there is a reluctance on the part of the vessels to transmit materials across the vessel walls into the brain substance. Just what the nature of this barrier is, what its mechanism of function is, and what its precise anatomical location is are as yet unknown, but the barrier would have to be localized either in the subendothelial

structures or in the immediate perivascular tissues where the brain substance itself establishes the barrier.

The problem of radiation response in the central nervous system is much more complex than it would first appear to be. Evidence seems to indicate that the total dose, the dose rate, and the volume irradiated all play very significant roles in the nature of this radiation response. Total doses in excess of 10,000 rads appear to produce very definite, primary-effect lesions within the principal neuronal cell components, and these changes may precede any observable response in the vascular system. On the other hand, doses in the range of 1000 to 3000 rads produce no well-defined cytopathology in these cells, but vascular injury develops rapidly. At the same time, it has been shown that a high dose rate has a much greater tendency to produce primary injury within the nerve cells than does the same total amount of radiation given at a much lower rate. And, finally, the volume of brain irradiated also is a factor in that the greater the volume, the more likelihood that edema will develop, which in turn may produce neurological manifestations.

The mechanisms underlying the very early deaths are poorly understood. The possibilities are as follows:

1. There is an immediate and direct compositional effect upon the neuronal cells or their synapses which so far has remained undetected by even the most sophisticated analytical methods.
2. Functional block occurs at some point in the conductivity system.
3. A toxic substance is elaborated within the matrix of the brain.
4. The injuries that are known to be present in the vascular channels may permit transmittal of substances that produce secondary injury in the brain.
5. There is the complicating factor of a variable edema, which is largely perivascular in original location.

None of these possibilities, either individually or in combination, have satisfactorily explained the rapid and fulminating course of the so-called central nervous system syndrome. For that matter, there has also been insufficient evaluation of the possible role in the total-body response from the acute irradiation of the pituitary body and other organs and structures contiguous with or apposed to the brain.

MICROVASCULAR SYSTEM

Evaluation of the histopathology of acute whole-body irradiation would be incomplete without an accounting of those supportive cells and substances common to all organized tissues. The connective-tissue cells and their associated fibers and matrices are considered to be relatively unresponsive to irradiation. At those dose levels significant to the acute radiation syndromes and within the relevant time periods, little, if any, visible manifestation of radiation injury would become apparent. In contrast to this essentially passive role, the microvascular structures, which are generally considered an integral component of the supportive compartment, are subject to a variable and dose-dependent response that may amplify the direct radiation injuries incurred by the principal parenchymal cells they nourish.

Histology of the Microvascular System

The smallest functional unit of the vascular system is the capillary. This is a tubal structure formed by endothelial cells supported by a fine reticular mesh and is generally interposed as a plexus connecting small arterioles with venules. The capillaries range between 8 and 12 μm in diameter and thus provide passage for formed blood elements only if they flow in single file.

Closely allied with the blood capillaries in both structure and histological location are the fine lymphatics. They are not as uniform in caliber as the capillaries, and they do not have the same degree of reticular support. Because these lymphatics are not of critical importance to the life processes of the associated principal parenchymal cells, their compromise is of little clinical significance in relation to the acute radiation syndromes.

There are a few specialized microvascular retia, such as the capillaries of the renal glomerulus inserted between the afferent and efferent arterioles, the venous sinusoids of the anterior pituitary, and the complex sinusoidal system between the afferent and efferent lymphatics in the lymph nodes.

It is pertinent to the pathogenesis of the acute radiation response to include within the microvascular system the controversial precapillaries and the small arterioles. The precapillaries are an intermediate form between the histologically distinct and relatively complex arteriole and the structurally simple capillary. These precapillaries may range in diameter up to 40 μm with the lumens accommodating a substantially greater flow of formed blood elements than the capillary. The basic endothelial tube is variably and discontinuously supported and encircled by smooth-muscle fibers and connective-tissue elements. The rationale for incorporating the precapillary and small arteriole as components of the microvascular system is their equivalent cell responses and the relatively small caliber of the lumens which may be readily compromised by the endothelial swelling and perivascular compression.

The Effect of Radiation on the Microvascular System

The vascular system, in general, was long considered to be relatively resistant to radiation and of clinical concern only as a primary factor in the development of late tissue changes. Recently, increasing evidence has implicated the acute alterations in the microvascular component as a significant factor in the enhancement of the direct radiation injury in the associated primary parenchymal cells.

For reasons as yet incompletely understood, the endothelial cells of the capillaries and precapillaries appear to be more responsive to radiation than those of the larger vessels. It has also been observed that the alteration of the endothelium in those tissues prone to more severe and rapid effects in the principal cell components is more pronounced than in those tissues displaying less severe and more slowly developing effects. This discrepancy suggests an agent derived from the injured or dead principal cells which

augments or amplifies the direct action of the radiation on the endothelium.

The earliest visible change is that of endothelial cell swelling, which may involve both nucleus and cytoplasm. In the capillaries this may constrict the lumens so as to effectively prohibit or substantially decrease the flow of blood. This impedance of normal circulation may cause a backup of blood locally producing hyperemia and the increased likelihood of fluid transudation through the associated damaged vascular barrier. This nonspecific endothelial swelling may be transient with reversion to a normal state before any significant local ischemia becomes effective. On the other hand, the injury may be sufficient and of long enough duration to produce necrosis of the endothelial cells with possible thrombus formation, extravasation of formed and fluid blood elements, and localized ischemia in the parenchyma.

The precapillaries and some of the smaller arterioles may also react acutely to the radiation with swelling of both endothelial and smooth-muscle components. Vacuolation of the latter cells commonly occurs with the larger doses of radiation, and necrotizing endarteritis may be a rapidly developing complication. The sinusoids present in many of the more richly vascular structures are lined not by endothelial cells but by flattened fixed macrophages that are relatively unresponsive to radiation.

Because of the random distribution of the ionizing events within the tissue, the relatively small and widely spread population of endothelial cells, and an assumed variation in individual cell sensitivity at the moment of the event, the subsequent histopathology will not be uniform in its distribution but will be characterized by intermittent and variable alterations along the lengths of the vessels.

In the early postirradiation period, particularly when the dose has been only moderate, the vascular alterations are often inconspicuous, and it is difficult to assess the nature and magnitude of the role these lesions may play in the progression of pathology within the affected tissue. Of primary consideration is the relative and frequently transient local ischemia produced by the swollen or degenerating endothelial cells with or without associated thrombi and possible capillary compression from exudative fluids. This deficiency of blood supply aggravates the direct radiation injury of the parenchymal cells and also tends to inhibit early repair mechanisms.

As the magnitude of the acute dose is increased, the number of focal occlusive vascular lesions increases proportionately until virtually all ramifications in the exposed capillary network are compromised and there is ischemia in the tissues supplied by this particular plexus. If this large dose is protracted or fractionated, the resultant changes will be more insidious in their development. This condition promotes progressive hypoplasia of the principal cells and an expanding interstitial fibrosis.

SKIN

Cytokinetics of the Skin

The skin has two principal structural divisions—epidermis and dermis. The outer layer, or epidermis, is basically a stratified squamous epithelium. It varies greatly in depth over different areas of the body—from 0.05 mm or less over the abdomen to greater than 1.0 mm on the densely cornified palmar surface.

There are four distinct strata in the epidermis: germinal, granular, clear, and cornified. The basal layer in the germinal stratum consists of cylindrical cells polarized more or less perpendicularly to the thin basement membrane that separates epidermis and dermis. Under normal conditions these cells proliferate at a steady rate to replace those cells being continually sloughed from the epidermal surface. The remaining cells of the *stratum germinativum* are irregularly polyhedral in configuration and become progressively flattened as the granular stratum is approached. In the unstressed state mitotic activity is much less here than in the basal-cell layer, but it can be increased upon demand. All cells of the germinal stratum are connected by intercellular bridges or interconnecting spinous processes that span the prominent intercellular gap.

The granular stratum and clear stratum represent transitional stages in the cornification of the epidermal cells and may be entirely lacking in areas of very thin epidermis. In the granular layer the epidermal cells are flattened, the nuclei are pale and may be seen in varying phases of lysis, and droplets of keratohyaline occur in the cytoplasm. No cell division occurs in this stratum, and the intercellular spaces are markedly narrowed. In the clear stratum distinct cell boundaries are preserved; however, only scattered remnants of nuclear structure exist. To all intents and purposes, these are dead epidermal cells. The cytoplasm contains droplets of eleidin.

The cornified stratum is the final stage in the functional cycle of the epidermis. It consists of layers of very flattened and elongated cornified "cells." The superficial layers are constantly being sloughed off.

This multilayered epithelium of a continuous-cell-renewal type is nourished by perfusion through the intercellular spaces. There are no nutrient capillaries within the epidermis; however, there is a rich vascular bed in the subjacent dermis.

One other cell type should be mentioned in connection with the epidermis. Along the undersurface of the basal-cell layer and projecting into the dermis are richly pigmented cells of neural crest origin, the melanocytes. These cells, through a specific oxidative action of tyrosinase, elaborate melanin pigment, which is then transferred to the proliferating epidermal cells to eventually be distributed as a fine cytoplasmic dust.

The dermis may be arbitrarily divided into three poorly defined zones. The relative thickness of each layer will vary according to body area much as the structure of the epidermis. The outer zone is referred to as the papillary layer. It is the narrowest of the dermal divisions and is characterized by projecting papillae that extend into the epidermis. It is composed of a fine mesh of elastic fibers, loosely distributed bundles of collagen, and a network of vascular loops.

The principal dermal division, the reticular layer, is marked by a dense zone of interlacing collagen bundles running at various angles to the surface epidermis but generally oriented parallel to the surface. Elastic fibers are

abundant and are particularly conspicuous about the hair follicles and accessory skin glands.

The deep dermal zone, or hypodermis, is poorly delineated and merges indistinctly with the reticular layer. The loose connective-tissue matrix contains a variable amount of fat, the deeper portions of the hair follicles, nerve bundles, and penetrating vessels.

The hair follicles are deep invaginations of the surface epithelium that culminate at the bases in bulbous expansions encasing connective-tissue papillae. Surmounting the papillae are the proliferating epithelial cells responsible for the continuous propagation of the hair shaft.

The sebaceous glands are situated in the dermis with their relatively short excretory ducts emptying into the hair follicles. The modified cells comprising the functional portion of this holocrine gland are derived from the epithelial cells situated near the excretory duct. The sweat glands are simple coiled glands situated usually deep in the reticular zone of the dermis. The unbranched excreting duct courses outward to empty directly upon the skin surface. The plump, wedge-shaped cells of the secretory portion rest upon a layer of myoepithelial cells, which in turn are in apposition to the relatively thick basement membrane of the gland.

The Effect of Radiation on the Skin

The skin is not directly involved in the evolution of the acute radiation syndrome although in two of the five cases reviewed here an upper extremity was in close proximity to the point source and received an unusually large amount of predominant low-energy radiation (40,000 to 50,000 R).

The generative cells of the epidermis and its accessory structures are moderately responsive to the actions of radiation (Fig. 1.7). With relatively low doses (100 to 200 R) there is transient mitotic arrest and some degree of cell degeneration in the proliferative component. These effects are of no clinical import because the mitotic block is brief with no significant compromise of the cell-renewal process. As the total acute dose is increased, however, the cessation of mitosis and degeneration of proliferative cells are extended to the point where the replenishment of cells necessary to perpetuate the integumental barrier is impaired. At the same time, a separation of the hair root from the papilla is developing. Although the hair shaft becomes physically separated at the base, there is enough adherence to the wall of the follicle to resist depilation for a brief period of time. When the applied dose exceeds 700 R, this depilation may become permanent depending in part upon the body area involved; e.g., the hair of the scalp is more sensitive than the eyebrows or eyelashes.

The sebaceous glands, which lie in close proximity to the hair follicles, are subject to a similar degree of sensitivity and are functionally suppressed within a week of the radiation. Distinctive histological changes may be delayed for several more weeks with persistence of these structures even after the hair follicles have collapsed and become atrophic.

The sweat glands are more resistant to the radiation although variable reduction in function may be observed to roughly coincide with the depilation and cessation of sebaceous-gland function. Although their functional capacity may be essentially nullified with high doses, these glands remain physically intact and identifiable even when most other skin structures have been deleted.

To produce a severe acute dermatitis, large doses of radiation are required—at least 2000 R. The basal-cell layer loses proliferative capacity and a significant proportion of the cells degenerate. Other cells of the germinal stratum exhibit nuclear and cytoplasmic vacuolation, cell swelling, and cytolysis. Intraepidermal blisters develop—frequently in the region of the basal-cell layer—which may enlarge and coalesce to form bullae. There may be rapid slough of the epidermis under these circumstances or a more protracted process of hypoplasia and ulceration based mainly upon enhanced attrition without compensatory cell renewal.

The irradiated melanocytes may respond in two ways. With moderate doses, the tyrosinase activity may be temporarily increased with the production and dissemination of excessive amounts of pigment. This accounts for the darkening of the skin in the affected areas. As the dose absorbed increases, however, the enzyme activity is suppressed, and the melanocytes are destroyed or sloughed off, hence the areas of blanching in heavily irradiated skin. Both these processes may take weeks or months to develop and are characteristic of the more chronic form of radiation dermatitis.

Meanwhile, in the underlying dermis, progressive degeneration is developing in the accessory structures as noted previously. Thickening, condensation, some apparent fracturing of the collagen bundles, and some fragmentation of the elastic fibers occur. Of significance is the endothelial swelling, especially in the smaller vessels, which causes some degree of luminal constriction and a variable relative focal ischemia. Edema may be severe, and an inflammatory infiltrate is often present.

Because very high doses are required for the development of severe acute skin injury and there is a lag time of several days to weeks for most of these effects to become manifest, especially in the dose range pertinent to total-body irradiation lethality, this syndrome is not of particular clinical import. The occult presence of impending epidermal change is, however, heralded by the obvious depilation. Where a particular segment of the body has received an additional very high dose, these events within the skin may be disproportionately severe and may develop in a matter of days, thereby contributing to the overall debility of the total-body irradiation.

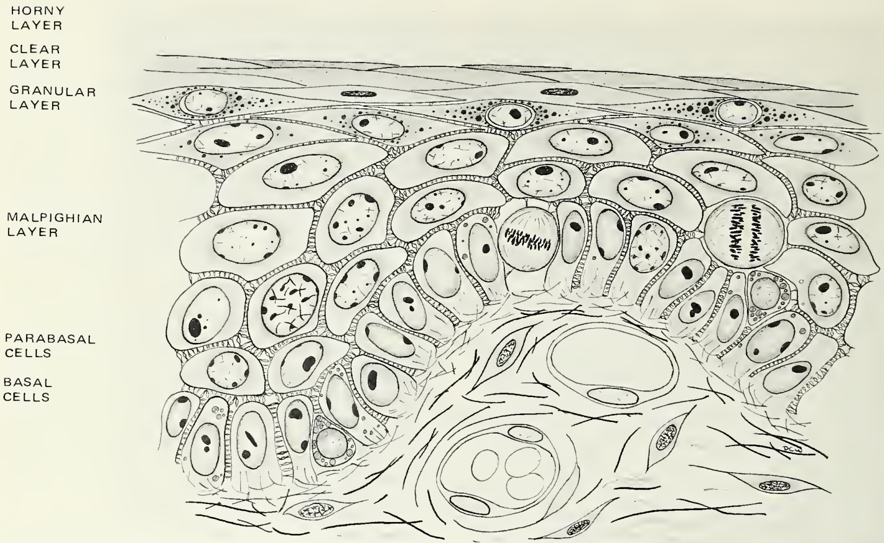
REFERENCES

Andrews, J. R., 1968, *The Radiobiology of Human Cancer Radiotherapy*, W. B. Saunders Company, Philadelphia.

Arnold, A., P. Bailey, and R. A. Harvey, 1954, Intolerance of the Primate Brainstem and Hypothalamus to Conventional and High Energy Radiations, *Neurology*, 4: 575-585.

Bacq, Z. M., and P. Alexander, 1961, *Fundamentals of Radiobiology*, Academic Press, Inc., New York.

Behrens, C. G., (Ed.), 1964, *Atomic Medicine*, Williams & Wilkins Company, Baltimore, Md.



(a)

(b)

Fig. 1.7 Skin. (a) Normal skin. (b) Early radiation effects.

Berdjis, C. C., (Ed.), 1970–1971, *Pathology of Irradiation,* Williams & Wilkins Company, Baltimore, Md.

Bloom, W., and M. A. Bloom, 1954, Histological Changes After Irradiation, in *Radiation Biology, High Energy Radiation,* Vol. 1, A. Hollaender (Ed.), p. 1091, McGraw-Hill Book Company, New York.

Bond, V. P., T. M. Fliedner, and J. O. Archambeau, 1965, *Mammalian Radiation Lethality,* Academic Press, Inc., New York.

Brent, R. L., 1963, *Proceedings of the International Symposium on Effects of Ionizing Radiation in the Reproductive System,* Colorado, Pergamon Press, Inc., New York.

Carlson, W. D., and F. X. Gassner (Eds.), 1964, *Effects of Ionizing Radiation on the Reproductive System: Proceedings of an International Symposium Held at Colorado State University,* The MacMillan Company, New York.

Casarett, A. P., 1968, *Radiation Biology,* Prentice-Hall, Inc., Englewood Cliffs, N. J.

Clemente, C. D., and E. A. Holst, 1954, Pathological Changes in Neurons, Neuroglia, and Blood–Brain Barrier Induced by X-Irradiation of Heads of Monkeys, *AMA Arch. Neurol. Psychiat.,* 71: 66-79.

Eddy, H. A., and G. W. Casarett, 1968, Intestinal Vascular Changes in the Acute Radiation Intestinal Syndrome, in *Gastrointestinal Radiation Injury,* Monographs on Nuclear Medicine and Biology, Excerpta Medical Foundation, M. F. Sullivan (Ed.), Reidel, Dordrecht, Netherlands.

Fanger, H., and C. C. Lushbaugh, 1967, Radiation Death from Cardiovascular Shock Following a Criticality Accident, *Arch. Pathol.,* 83: 446-460.

Fletcher, G. H., 1966, *Textbook of Radiotherapy,* Lea & Febiger, Philadelphia.

Haley, T. J., and R. S. Snider (Eds.), 1962, *Response of the Nervous System to Ionizing Radiation,* Academic Press, Inc., New York.

Harris, R. J. C., 1963, *Cellular Basis and Aetiology of Late Somatic Effects of Ionizing Radiation,* Academic Press, Inc., New York.

Hempelmann, L. H., H. Lisco, and J. G. Hoffman, 1952, The Acute Radiation Syndrome: A Study of Nine Cases and a Review of the Problems, *Ann. Intern. Med.,* 36: 279.

Hollaender, A., 1954–1956, *Radiation Biology,* 3 volumes, McGraw-Hill Book Company, New York.

Jammet, H., et al., 1959, Etude de six cas d'irradiation totale aigue accidentelle, *Rev. Fr. Etud. Clin. Biol.,* 4: 210-225.

Karas, J. S., and J. B. Stanbury, 1965, Fatal Radiation Syndrome from an Accidental Nuclear Excursion, *New Engl. J. Med.,* 272: 755-761.

Lacassagne, A., and G. Gricouroff, 1958, *Action of Radiation on Tissues: An Introduction to Radiotherapy,* Grune and Stratton, Inc., New York.

Langham, W. H., (Ed.), 1967, *Radiobiological Factors in Manned Space Flight,* National Academy of Sciences–National Research Council, Washington, D. C.

Liebow, A. A., S. Warren, and E. DeCoursey, 1949, Pathology of Atomic Bomb Casualties, *Amer. J. Pathol.,* 25: 853-1029.

Manual on Radiation Hematology, 1971, Technical Report Series 123, International Atomic Energy Agency, Vienna (STI/DOC/10/123).

Moss, W. T., 1965, *Therapeutic Radiology,* The C. V. Mosby Company, St. Louis, Mo.

Oakes, W. R., and C. C. Lushbaugh, 1952, Course of Testicular Injury Following Accidental Exposure to Nuclear Radiation: Report of a Case, *Radiology,* 59: 737-743.

Oughterson, A. W., and S. Warren, 1956, *Medical Effects of the Atomic Bomb in Japan,* McGraw-Hill Book Company, New York.

Pizzarello, D. J., and R. L. Witcofski, 1967, *Basic Radiation Biology,* Lea & Febiger, Philadelphia.

Radiation-Induced Cancer, 1969, Symposium Proceedings, Athens, April 28–May 2, 1969, International Atomic Energy Agency, Vienna (STI/PUB/228).

Rubin, P., and G. W. Casarett, 1968, *Clinical Radiation Pathology,* 2 volumes, W. B. Saunders Company, Philadelphia.

Saenger, E. L., February 1963, Medical Aspects of Radiation Accidents: A Handbook for Physicians, Health Physicists, and Industrial Hygienists, USAEC Report TID-18867, University of Cincinnati.

Shipman, T. L., et al., 1961, Acute Radiation Death Resulting from an Accidental Nuclear Critical Excursion, *J. Occup. Med.,* 3: 146-192.

Sullivan, M. F., (Ed.), 1968, Gastrointestinal Radiation Injury: Report of a Symposium Held at Richland, Washington, 1966, Excerpta Medica Foundation.

Szirmai, E., (Ed.), 1965, *Nuclear Hematology,* Academic Press, Inc., New York.

Taliaferro, W. H., L. G. Taliaferro, and B. N. Jaroslow, 1964, *Radiation and Immune Mechanisms,* Academic Press, Inc., New York.

Thoma, G. E., and N. Wald, 1959, Diagnosis and Management of Accidental Radiation Injury, *J. Occup. Med.,* 1: 421-447.

Upton, A. C., 1969, *Radiation Injury: Effects, Principles and Perspectives,* The University of Chicago Press, Chicago.

Van Cleave, C. D., 1963, *Irradiation and the Nervous System,* Rowman & Littlefield, Inc., New York.

Watten, S., 1961, *The Pathology of Ionizing Radiation,* Charles C Thomas, Publisher, Springfield, Ill.

CLINICAL CASE SUMMARIES

Case A (905226)

At the time of the accident this 38-year-old male was engaged in a plutonium-recovery activity. Residues of waste material containing relatively small concentrations of plutonium were treated chemically to salvage the plutonium. Some of this material had been transferred to a large enclosed stainless-steel processing tank that already contained an emulsion with plutonium in it. He stepped up on a low platform, looked through the view port of the vat, and pressed the switch to start the stirring mechanism. Almost instantaneously a critical configuration was achieved when the plutonium concentrations within the two liquid phases were mixed. At this moment it was estimated that he had received 900 rads of neutron and 4000 rads of gamma radiation as an average whole-body exposure. The dose to the trunk alone was about 12,000 rads. He fell from the low step and immediately ran from the building. He was reported to be ataxic and disoriented and kept repeating, "I'm burning up!"

Two fellow workers who had been working in adjacent rooms immediately came to his assistance. They assumed there had been a chemical accident and helped him to an emergency shower station. Alpha monitors were available; however, there were no gamma detectors in the area because a criticality accident had been considered to be impossible. A radiation alarm in a building about 175 ft away had been activated by the nuclear excursion.

At this time, within a few minutes of the accident, he was unable to stand unaided and lay on the floor in a

semiconscious state. The area duty nurse arrived and determined that the man was in shock but inconsistently had a general healthy pink suffusion of the skin. On admission to the emergency room of the medical center, approximately 30 min after the accident, he was severely hypotensive with a barely audible heart beat of 160 per minute, incoherent, and retching and vomiting. His skin had become dusky reddish-violet, and his lips and nail beds were markedly cyanotic. The conjunctivae and sclerae were very hyperemic. He seemed somewhat hyperactive and required restraint.

Shortly after admission he had forceful watery diarrhea with no evidence of blood. The feces and vomitus showed slight radioactivity when checked by a survey meter and his body surface read 15 mR/hr. Supportive measures resuscitated him from the shock state, and he began to complain of severe abdominal cramps although this was not associated with the presence of any abnormal auscultative findings.

About 2 hr after the accident, he was resting reasonably comfortably in shock position and in an oxygen tent. Physical examination did not reflect the lethality of his exposure. There was persistent hypotension, tachycardia, erythema (most intensive anteriorly), edematous hands and forearms, scleral congestion, and a fever of 103°F. The high temperature persisted for 6 hr and then rapidly declined to normal levels where it remained. He was unable to tolerate removal from the oxygen tent, and whenever intravenous fluid administration was interrupted his hypotension worsened. This latter situation led to an excessive amount of intravenous fluid.

A sternal marrow aspiration was performed about 24 hr after exposure. The material recovered was unusually watery, and smear preparations disclosed an almost acellular marrow. This finding, along with the initial high fever and the rapid, almost total, lymphopenia, bespoke the lethal nature of his acute illness.

In the latter portion of his fulminating clinical course he became increasingly restless and apprehensive and the abdominal pain became difficult to control. During the final few hours it became almost impossible to maintain administration of parenteral fluids or oxygen by mask. He was diaphoretic and hypotensive with slowing, shallow respirations. He died about 35 hr after the accident.

Case B (1164946)

A 38-year-old male who worked in a ^{235}U recovery plant was pouring a mixture containing waste ^{235}U from a large cylinder into a vat containing sodium carbonate. As this transfer neared completion, a critical geometry was attained and an intense nuclear excursion occurred. The worker stated that there had been a flash of light and that he had been forced backward. It was later estimated that he had received an instantaneous whole-body exposure of 2200 rads of neutron and 6600 rads of gamma radiation. He ran from the laboratory to an emergency treatment building about 200 yd away, discarding his clothing along the way.

The basic circumstances differed from case A only in that case B had received radioactive spillage whereas there was no contamination in case A. At this time he was complaining of headache and abdominal cramps, vomiting and had an uncontrolled watery bowel movement. He was taken to a nearby hospital but was not admitted and was forced to go to a much more distant medical center where he was received about 1 hr and 43 min after the accident.

On admission the headache and abdominal cramps were still the main complaints. He was diaphoretic; blood pressure slightly elevated, 160/80; temperature, 100.4°F; pulse, 100 and regular; and respirations, 20. His skin color was good. The initial physical examination was remarkably normal.

Over the subsequent few hours the blood pressure steadily declined and the pulse rate increased; however, the use of vasopressors maintained the values within acceptable limits. The patient felt well at this time (about 11 hr after the accident). His temperature had risen to 102°F, and there was increasing edema and erythema of the left forearm and hand that had been holding the transfer cylinder.

During the final hours of his illness, he became progressively restless and apprehensive. He was more dyspneic, the left upper extremity became severely swollen, and there was increasing erythema of the left side of the face and a left conjunctivitis. His visual acuity had become markedly decreased. The hypotension became refractive to all therapeutic measures, his renal output ceased, and he became disoriented and poorly responsive. He died 49 hr following the accident.

Case C (1147724)

An experimental nuclear reactor (critical assembly) was being used to evaluate the properties of fissionable materials. By achieving a certain mass of this material or by particular geometric configuration it becomes possible for an excursion chain reaction to develop with the release of large amounts of radiation. Because at this particular time there was a great urgency to vigorously pursue these fundamental reaction studies and because there was still little remote-control equipment available, it was unavoidable that the operators at times be in close proximity to the critical assembly. It should be pointed out that this form of nonexplosive nuclear excursion gives off neutrons, gamma, and beta rays. The relative lack of shielding and the close proximity of the operator implied exposure to all three radiations. Some of the very low energy beta radiations were blocked by the minimal assembly structure, but a large quantity of soft radiations came through to be absorbed by that portion of the body closest to the reactor.

This 32-year-old man was touching the assembly with his left hand when the accident occurred. Because of the varied characteristics of the radiations emanating from the unit, it is all but impossible to arrive at an accurate average whole-body exposure. It was determined, however, that his hand received upwards of 15,000 R of soft X rays at the same time his body absorbed about 1930 R of 80-kV X rays and 114 R of gamma rays. He was admitted to the hospital about 1 hr after the accident. He was apprehensive and nauseated. He vomited several times during the first few hours. An initial examination disclosed a temperature

of 100.2°F; pulse, 104; respirations, 20; and blood pressure, 110/70. No other abnormal findings were recorded.

His general condition appeared good throughout the first 5 days of his illness although his upper extremities responded rapidly and dramatically to the intense exposure to low-energy radiations. This began with erythema, edema, and cyanosis of the nail bed of the left thumb accompanied by numbness and tingling. Within 24 hr of the exposure, the entire hand and forearm were severely edematous and painful. By the *3rd* day this arm had a very firm wax-like consistency and appearance, and there were large draining bullae on the hand. Even though the arm was continuously packed in ice, the swelling and dusky coloration extended to the axilla. There was never any evidence of infection in this severely compromised extremity. The right hand and forearm received considerably less irradiation; thus there was a proportionately less severe clinical reaction.

After the initial gastrointestinal unrest, which lasted several hours, he had no further difficulty in this regard until day 6 when he again became nauseated, vomited, and had a distended and quiet abdomen. This ileus was generalized and refractive to conservative treatment although a nasogastric suction tube seemed to control the stomach and small bowel distention. Although his stools up to this time had been formed and nonguaiac reactive, on the final stormy 3 days they were liquid, involuntary, and guaiac positive. The renal output was adequate until the final day when there was no recorded urine output. Urinalysis throughout his illness had disclosed increasing albumin, erythrocytes, leucocytes, and casts. His NPN on the final day had risen to 161 mg%.

There was a distant, subdued quality to the heart beat on the *7th* day, and a faintly audible friction rub appeared. There was no identified cardiac enlargement. Although pulmonary auscultation remained clear throughout his illness, his respirations on the final day were shallow and rapid, and an oxygen tent was required.

On the *5th* day there was a marked decline of his leucocyte count, and on day 6 he developed a sharp temperature rise to 102°F. His fever continued to range even higher until his death. Terminally he became comatose and died on the *9th* day after the accident.

Case D (1147723)

The circumstances of the accident were almost identical to those encountered in case C (1147724). This 26-year-old male was touching the critical assembly with his right hand when the nuclear excursion occurred. It is estimated that this hand received between 20,000 and 40,000 R of low-energy radiation. His other hand also in proximity to the reactor absorbed approximately 5000 to 15,000 R. The remainder of the body, particularly the trunk, received about 480 R of 80 kV X rays and 110 R of gamma rays. It is probable that this whole-body exposure was nonuniform in its distribution, and there were no means of reliably determining the doses to different parts of the body.

His previous medical history was essentially normal except for a borderline functional heart condition diagnosed as Wolff-Parkinson-White's syndrome and characterized by short P-R intervals and prolonged QRS times. There had been only one known episode of tachycardia.

Upon admission to the hospital, 25 min after the accident, his only complaints were numbness and tingling of both hands. The physical examination was remarkably negative except for the upper extremities. The right hand was pale and swollen, and there was swelling of his left thumb and index finger. About 90 min after the accident he had nausea with retching and vomiting and epigastric cramping. This gastric distress continued through the *1st* day, with nausea and hiccoughing persisting through the *2nd* day. Thereafter, until the final several days of his illness, his appetite was good and he ate adequately. During the first 24-hr period, he was noted to be variably hypotensive and had dyspnea on even slight exertion. On the *5th* day his temperature, pulse, and respirations became persistently elevated and continued a steady rise until his death on the *25th* day following the accident. On the *10th* day he once again had nausea and began to complain of cramping abdominal pains. There was moderate distention and some deep tenderness in the right upper quadrant. This gastrointestinal problem persisted and was severe for several days. On the *12th* day this difficulty was compounded by the development of a severe stomatitis with pseudomembrane formation and thick tenacious mucus making food intake all but impossible. His fluid input was maintained parenterally until this problem diminished during the *3rd* week. He had a severe episode of tachycardia on the *15th* day following the administration of whole blood and intravenous fluids. This condition ceased abruptly after about 24 hr; however, there was residual relative hypotension, apparent cardiac enlargement, and a detectable friction rub. His pulmonary function did not appear to be compromised although respirations became rapid and shallow terminally. His renal function showed no evidence of impairment during his illness.

The severe injury to his upper extremities deserves more detailed description in that the intensity of the response undoubtedly had some bearing upon the general physical reserve. The swelling of the right hand increased markedly during the first 24 hr, and during the subsequent several days this edema spread to involve the entire extremity. The hand rapidly became numb to sensation, dusky in color, and cool to touch with the development of epidermal blisters. The left hand and forearm had responded more slowly with the appearance of erythema and moderate edema, which persisted for several days and then regressed. It became necessary to remove the dead skin over the surfaces of the right hand and forearm in order to alleviate some of the pressure pain. During the *3rd* week there was slow resolution of the edema and beginning demarcation of dead zones of the fingers, the appearance being that of dry gangrene.

It was not until the *3rd* day that erythema of the abdomen, thorax, and face developed. This increased in intensity and became sharply demarcated over the subsequent several days. Moist desquamation was evident during the *2nd* and *3rd* weeks; the denuded surfaces were exceedingly tender.

Epilation was first evident on the *17th* day and continued until the temples and frontal vertex areas were completely devoid of hair. Loss of beard was also present.

The progression of events indicated a continually increasing systemic toxicity much of which was probably due to the intensity of the epidermal and dermal injury of the extremities and abdomen superimposed upon severe compromise of the intestinal mucosa and a pancytopenia. He died on the 25*th* day.

Case E (AFIP 980029)

On the day of the accident, the reactor, which consisted of a core of 4000 kg of uranium, immersed in heavy water, was operating at subcritical levels and was being monitored by six persons all situated approximately equidistant from the reactor tank. A sudden power surge caused the reactor to become supercritical with a resultant burst of mixed neutron–gamma radiation. All personnel dosimeters were off scale, and the personnel immediately evacuated the area.

Severe nausea and intractable vomiting occurred within the 1*st* hour, followed by pallor, asthenia, and apprehension. There was some intermittent diarrhea during this initial phase, and facial erythema and conjunctivitis were observed in all individuals. There then ensued a latent period that continued until the end of the 3*rd* postexposure week. Although the general physical condition appeared satisfactory, such findings as stomatitis, weight loss, abdominal pain, headache, and variable emotional response occurred periodically throughout this so-called latent period.

There was epilation beginning on the 14*th* day. In view of the rather dramatic pancytopenia present in all six individuals, marrow transfusion was attempted. This individual, however, did not respond to this treatment, and, from the 14*th* day until death, he showed hemorrhagic manifestations in the form of epistaxis and gastric and pulmonary bleeding. There was apparent paralytic ileus, anuria, and jaundice beginning just prior to death on the 32*nd* day after the accident.

RADIATION HISTOPATHOLOGY OF REPORTED CASES

Case A (905226)

BONE MARROW. A low-power scan of the marrow reveals a severe depression of the hematopoietic component, with a resultant relative prominence of the fat cells and vascular sinusoids that show dilation and moderate congestion (Fig. 1.8). Of the residual nucleated elements, the dominant forms are the postmitotic maturing myelocytic and erythrocytic types and the large macrophage, which exhibits phagocytosis of cellular debris and hemosiderin pigment (Fig. 1.9). Also identified are monocytes and plasma cells in relative excess of normal ratios. There are scattered megakaryocytes disclosing variable nuclear alterations, such as condensation and homogeneity to the chromatin substance, vacuolation, and failure of continued nuclear division. A few large cell forms are present which morphologically resemble the more primitive elements of the hematopoietic series. Their lineage, however, is obscure, and their structure is atypical. Many other cells in varying states of degeneration defy accurate differentiation, and an overall infusion of amorphous cytoplasmic and nuclear debris is present.

SPLEEN. Certain distinctive histologic alterations are immediately apparent. There is a substantial decrease in the nucleated elements comprising the splenic parenchyma. The white pulp is for the most part well defined but reduced in volume and very characteristic in appearance (Fig. 1.10). These areas, normally densely populated by small lymphocytes, have undergone rapid and dramatic destruction of these principal cell components, giving the white pulp areas a "peppered" appearance. Almost all the small lymphocytes are in an advanced state of degeneration, with pyknotic and hyperchromatic nuclei, nuclear irregularity, and finally fragmentation of nucleus and dissolution of cytoplasm. These dying cells and the debris that they generate have been largely phagocytized by the active histiocytes of this area. These macrophages are very numerous and display unusual enlargement as a result of the engulfment of large quantities of cellular debris and the presence within the cytoplasm of large and irregular vacuoles (Fig. 1.11). There is a slight infiltration of the area by granulocytes.

The sheathed arteries display distinctive changes. They are relatively more prominent than under normal conditions owing to a combination of factors. As already indicated, the white pulp area is reduced in size as a result of the lymphocyte destruction. The walls of the sheathed arteries have thickened through a combination of histologic changes. The endothelial cells show a variable degree of swelling and some cytoplasmic vacuolation, and they are irregularly distributed along the luminal surface. Occasional clefts are formed beneath the endothelial cells which seem to lift these cells from the underlying intima. There is an irregular and focal deposition of dense hyaline substance in the subintimal zone along the lengths of these sheathed arteries. This thickening occasionally circumscribes the entire lumen although, more often than not, it is eccentric in location. There is a variable enlargement of the smooth-muscle cells within the vessel walls and an increase in the thickness of the adventitial portion of sheathed artery primarily as a result of separation of the individual connective-tissue elements. Occasionally, the additive effects of these processes result in almost total constriction of the lumen.

LYMPH NODE. Because of the nonuniformity of the whole-body exposure, there is also a distinctive variation in the responses of the variously situated lymphoid tissues to the radiation. However, in those portions of the thorax and trunk receiving the greatest proportion of the radiation, the changes are similar. There is an overall decrease in the small lymphocyte population, although this is not a particularly prominent effect at this early stage. It is apparent, however, that the vast majority of the small lymphocytes display a significant degree of pyknosis and karyorrhexis; and, in the reactive centers, this response is more pronounced, presumably owing to the increased cell sensitivity in this generative locus of the lymphocyte population (Fig. 1.12). At these germinal centers the pyknosis is extreme, and there is a great deal of nuclear and cellular fragmentation. Phagocytosis is very active as in the spleen with the

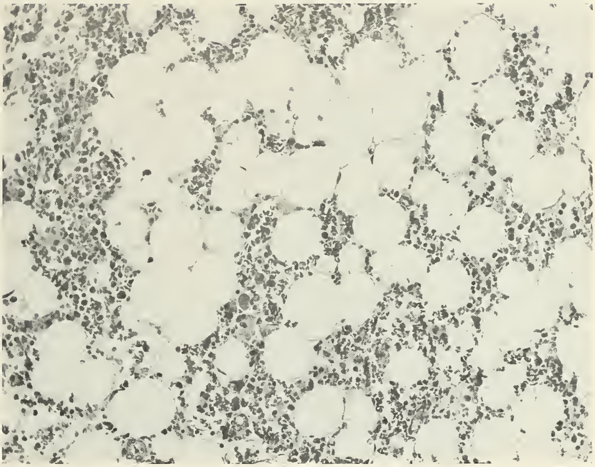


Fig. 1.8 Bone marrow. Hematopoietic depression.

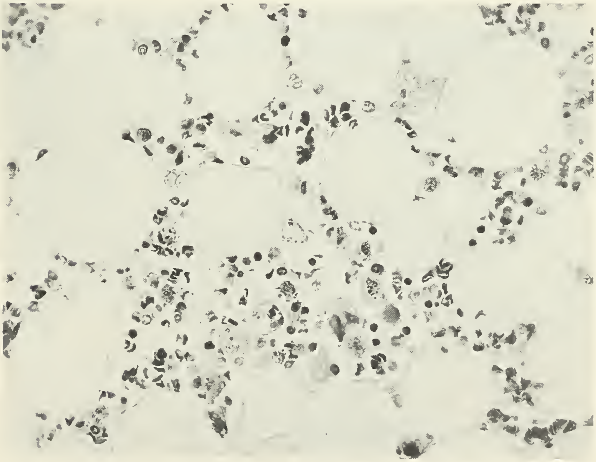


Fig. 1.9 Bone marrow. Degeneration of immature cells.

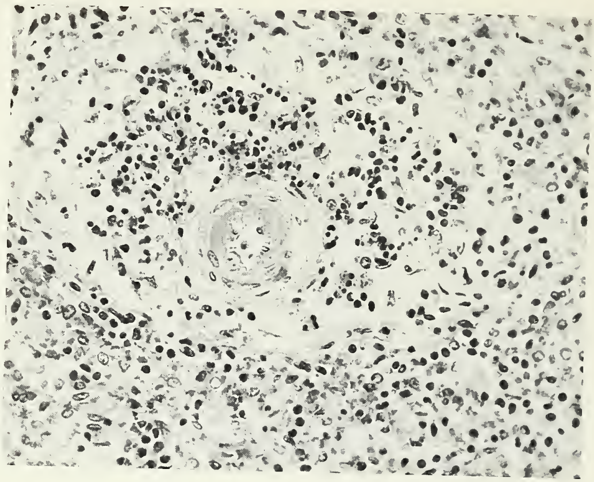


Fig. 1.10 Spleen. Lymphocyte destruction in white pulp.

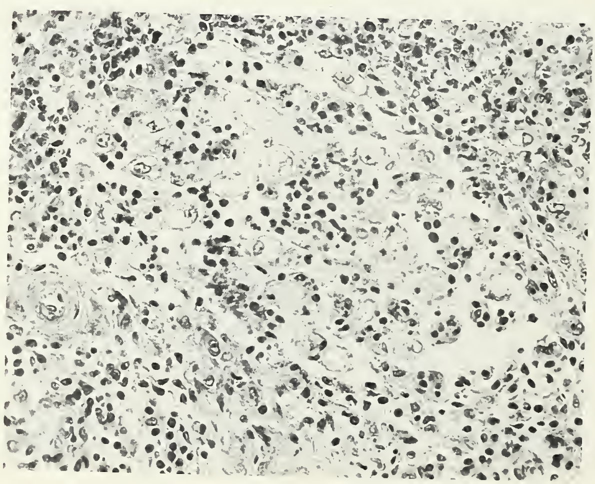


Fig. 1.11 Spleen. Phagocytosis of cell debris.

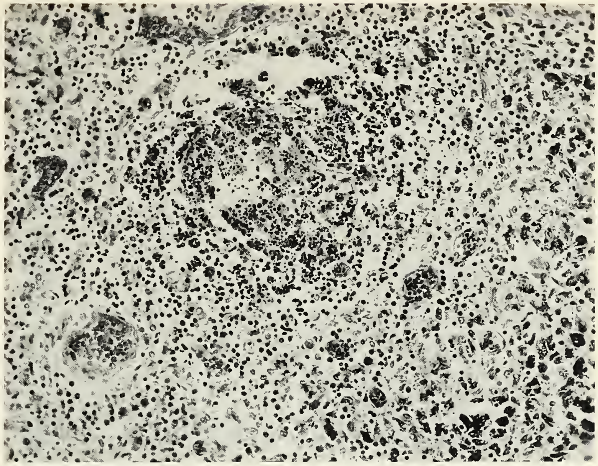


Fig. 1.12 Lymph node. Lymphocyte degeneration in germinal center.

majority of this debris already engulfed by the swollen macrophages (Fig. 1.13). Many of the static reticular cells do not show any specific morphologic features suggestive of radiation injury, although there is variable cytoplasmic vacuolation and, in some instances, pronounced vesiculation of the nuclei (Fig. 1.14).

THYMUS. A small amount of residual thymic parenchyma is distributed randomly in the mediastinal adipose tissue. There is a poorly defined division into cortex and medulla with a relative prominence of the epithelioid type of thymocyte. Although this gland is largely atrophic, there was apparently a significant population of small thymocytes which at this point has undergone almost total destruction through the action of radiation; the residual shrunken cells present small, densely hyperchromatic and fragmented nuclei (Fig. 1.15). Phagocytosis is not as prominent a feature here as it is in the lymph nodes and spleen, and removal of debris seems to be occurring at a much slower pace. Hassal's bodies are present and are not remarkable in appearance.

INTESTINE. No appreciable alteration occurs in the overall architecture of the mucosa of the small intestine. For that matter, at first examination this mucosa would appear to be well within normal limits. Upon closer scrutiny, however, certain points of interest are identified. With regard to the epithelium, there is a moderate decrease in the cell population of the crypts, particularly in the zones of proliferation. The remaining cells have a lower, more cuboidal profile, have broader bases, and many display a moderate degree of nuclear pleomorphism with some increased density and clumping of the nuclear chromatin (Fig. 1.16). This nuclear pleomorphism extends up into the maturation zones but does not spill onto the villi. The epithelial cells of the villi are within the normal range of morphologic variation. No significant changes are noted in the Paneth's cell population at the bases of the crypts. Mitotic figures are rare in the normally actively dividing crypt-cell population. Those few which are identified are distinctly atypical in configuration (Fig. 1.17). Active cell degeneration exceeds normal limits in only a few of the crypt areas, and the debris from the initial wave of cell destruction has been almost entirely removed. The lamina propria is strikingly devoid of lymphocytes, although there are some which persist and which show severe pyknosis as well as nuclear fragmentation. There is an unusual degree of separation of the connective-tissue fibers and the reticulin network both in the lamina propria and in the submucosa, which suggests moderate, interstitial edema. Some of the smaller vessels also exhibit swelling of not only the endothelial cells but also some of the smooth-muscle cells comprising the vessel walls. No hemorrhages and no unusual degree of vascular congestion are present. There is little variation in the magnitude of change among the various segments of the small intestine.

STOMACH. It is difficult to identify any alteration that might be related directly to the ionizing radiation; however, the total absence of cell division in the neck of the gastric glands is probably related. Some of the epithelial cells show condensation of the nuclear chromatin, and this is primarily seen in the parietal cells. There is a decrease in the cellularity of the lamina propria.

ESOPHAGUS. There are no noteworthy histologic features other than an absence of mitotic activity in the basal-cell layer of the esophageal epithelium and an early degenerative response in the very small focal lymphoid

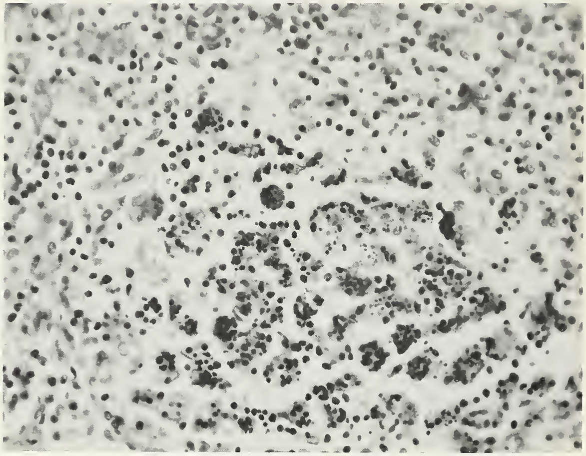


Fig. 1.13 Lymph node. Engulfment of cell debris by macrophages.

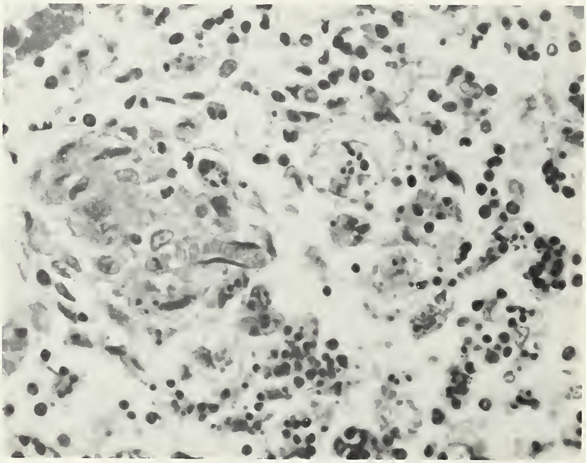


Fig. 1.14 Lymph node. Macrophages swollen with vacuoles and cell debris.

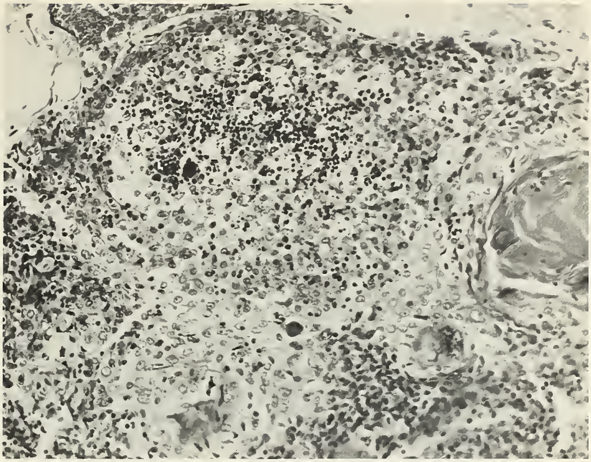


Fig. 1.15 Thymus. Degeneration of small thymocytes.

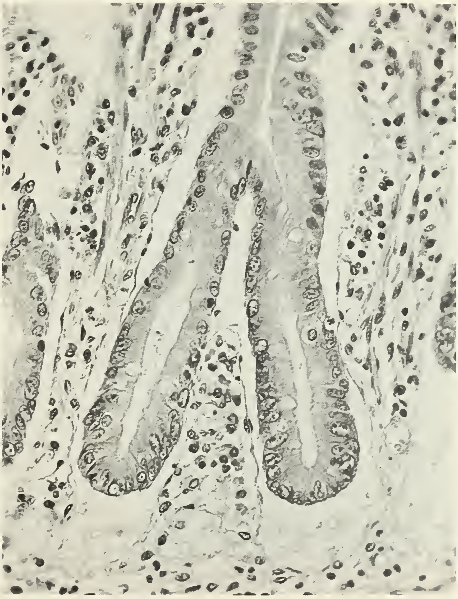


Fig. 1.16 Intestine. Moderate depletion of crypt cells.

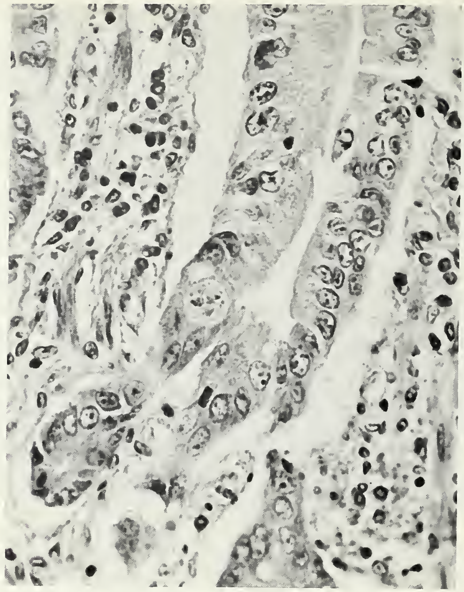


Fig. 1.17 Intestine. Infrequent and atypical crypt-cell mitosis.

aggregates in the submucosa. Changes in the small arterioles are equivocal.

LIVER. The principal hepatic cells and the duct epithelium exhibit no changes specifically referable to ionizing radiation. In some of the lobules, the peripheral hepatic cells display multinucleation but with uniformity of nuclear size. There is minimal thickening of arteriolar walls.

PANCREAS. A slight and variable amount of vacuolation occurs within the cytoplasm of the acinar cells. There are no nuclear changes of any significance. The cell components of the islands of Langerhans are unremarkable.

BRAIN. All divisions of the brain were sampled generously in an attempt to identify some evidence of specific radiation response. Although some equivocal alterations are seen, these are of an entirely nonspecific nature and are neither consistent nor conspicuous. There is a variable degree of separation of the parenchyma from the vascular walls but with no glial response or round-cell infiltrate. Occasional extravasation of a few erythrocytes may be observed about the smaller vessels. A rare neuron shows degenerative change with some satellitosis of the glial cells, and there is some slight and inconsistent thickening of the vessel walls due to variable swelling of endothelial and smooth-muscle cells.

TESTIS. A scan of the testicular parenchyma at low magnification discloses little deviation from the norm other than a widening of the interstitial spaces and the presence within the tubule lumens of cells other than mature spermatozoa (Fig. 1.18). Closer scrutiny reveals an early degenerative response in cells of the germinative epithelium identifiable as spermatogonia and spermatocytes. This damage takes the following forms:

1. Abnormal mitotic and meiotic divisions.
2. Clumping of the nuclear chromatin materials.
3. Vacuolation of both nucleus and cytoplasm.
4. Pyknosis.
5. Cell fragmentation.

The overall depth of the tubule epithelium is unchanged, and many of the spermatogenic cells exhibit no obvious cytopathology at this particular postexposure period. The resting or intermitotic cells and the postmitotic maturing spermatozoa appear entirely unaffected. It should be noted, however, that there is a decrease in the ratio of mature spermatozoa indicating continued expulsion through normal processes without adequate replacement (Fig. 1.19). The widening of the interstitial spaces appears due to an outpouring of moderate amounts of edema fluid. The interstitial cells of Leydig show no morphologic change. The small vessels exhibit swelling and vacuolation of the endothelial and smooth-muscle components.

HEART. The basic pattern of interlacing myocardial muscle fibers is undisturbed. There are no large dissecting hemorrhages; however, scattered throughout the myocar-

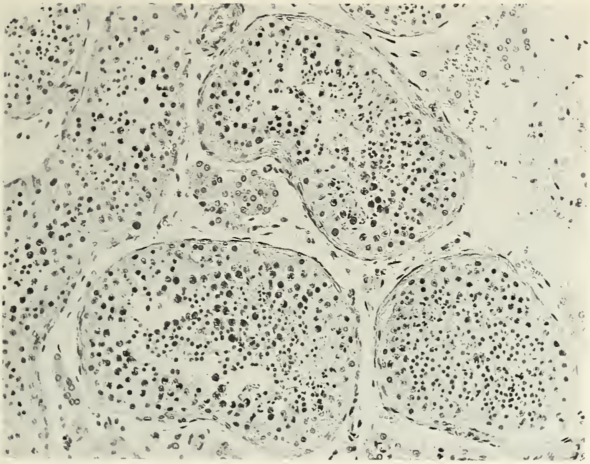


Fig. 1.18 Testis. Degenerating spermatogenic cells in tubules.

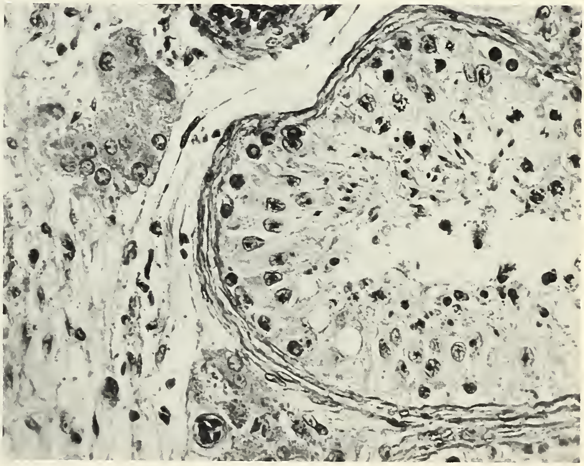


Fig. 1.19 Testis. Diminished spermatogenesis.

dium are focal extravasations of erythrocytes showing no specific predilection as to site of origin and no association with any histologic disruption or degeneration of the myocardial fibers. Many of the small arterioles are distinctly abnormal with swollen endothelial cells, smudgy and discontinuous intima, and enlarged and vacuolated smooth-muscle cells. It is not uncommon to see erythrocytes and granulocytes and some interstitial edema in the vicinity of these injured vessels. This histopathology is basically nonspecific; however, similar changes can be seen following high doses of localized radiation and the administration of vasopressor substances in large amounts. Similar vascular changes are identified also in the epicardial adipose and connective tissues indicating no specific predilection for the myocardium. There are some minute focal hemorrhages in the epicardial adipose tissue and occasional hemorrhage about small nerve radicals in this same area. One section of coronary artery shows a small infiltrative hemorrhage in the adventitia of one of the major coronary branches.

LUNG. Other than the mobilization of numerous macrophages to absorb organic debris within the alveoli, there is no notable histologic change. The pulmonary vasculature is not appreciably affected (Fig. 1.20).

KIDNEY. The nephrons have a normal histologic structure and anatomical interrelationship. In most of the glomeruli, there is variable, slight endothelial swelling without any observed occlusion of the capillary loops. The cells of the capsular and glomerular epithelium exhibit only occasional enlargement without any predilection as to site (Fig. 1.21). The epithelium of the proximal convoluted tubules displays a moderate, uniform granular swelling; however, there is no associated nuclear abnormality. The distal convoluted tubules are unremarkable, as are the collecting tubules. There is no edema or cellular infiltrate in the interstitial tissues. The vascular network including the afferent arterioles present only sporadic and equivocal intimal and endothelial swelling.

URINARY BLADDER. There is no significant histopathology.

SKIN. Radiation-induced changes are very subtle in the skin at this early postirradiation period. The epidermis has a normal histologic pattern, and the basal-cell layer is well polarized and shows no significant decrease in population. Mitotic figures are conspicuous by their absence, and occasional degenerating basal cells are present. In contrast, there is still a considerable residuum of active initial cell degeneration in the generative cells at the hair roots (Fig. 1.22). Glandular and ductal structures are entirely unremarkable. Vascular changes are equivocal, and there is no distortion of the collagen fibers in the outer dermis.

Case B (1164946)

BONE MARROW. A scan of the marrow at low magnification reveals all pertinent changes (Fig. 1.23). Of primary importance is the severe hypocellularity, particularly with respect to the hematopoietic cells, which under normal conditions would be a major component of the marrow. There is a compensatory dilation and congestion of the sinusoids and a relative prominence of the fat cells. Insofar as the hematopoietic compartment is concerned, most of the residual nucleated cells fall into three categories: postmitotic nucleated erythrocytes and granulocytes with folded, bilobate, or segmented nuclei; degenerating cells exhibiting pyknosis and karyorrhexis whose lineage cannot be accurately defined in paraffin section; and a variable infiltrate of monocytic cells and plasma cells. In addition, there are numerous swollen macrophages heavily laden with cellular debris. There are also infrequent immature cells of both granulocytic and erythrocytic series; however, most of these cells display morphologic atypism, and there is no evidence of any attempts by these cells to undertake additional division. Megakaryocytes are present but in significantly reduced numbers, and most of these show irregular condensation of the nuclear chromatin. Careful scrutiny of the residual hematopoietic cells reveals characteristic changes related to radiation including nuclear and cytoplasmic vacuolation, the presence of perinuclear clear coronas, binucleated cells, and cells containing small focal aggregates of ectopic nuclear material, karyomeres. The small nutrient arterioles, precapillaries, and capillaries coursing through the marrow areas exhibit swelling of the smooth-muscle components of the walls as well as enlargement of the endothelial cells (Fig. 1.24).

SPLEEN. The overall histologic pattern is one of compaction of the parenchyma (Fig. 1.25). There is a relative prominence of the trabeculations and the capsule with some irregular indentations of the latter. The sinusoids of the red pulp area have a collapsed appearance, being relatively devoid of erythrocytes, whereas some of the venous channels are dilated and packed with red cells. Other than the sinusoidal cells and the supportive connective tissue, the principal cell components are macrophages, monocytic cells, and a relatively small number of granulocytes. Because of the all but total depletion of the small lymphocyte population and removal of the debris, the white pulp areas are extremely difficult to distinguish and are usually best identified by searching the areas about the sheathed arteries (Fig. 1.26). These scavenged white pulp areas are now seen to consist of concentrically oriented reticular cells and associated connective-tissue cells, macrophages, occasional residual lymphocytes, and a few scattered granulocytes and plasma cells. There is some degree of continued phagocytosis in that a few of the macrophages contain vacuoles, cell debris, and occasionally an erythrocyte. The sheathed arteries are very similar in structure to those of case A (905226), with a variable amount of swelling of the endothelial cells, a smudginess to the intima with some focal deposition of hyalin-like material, vacuolation in the smooth-muscle cells of the vessel wall, and exaggeration of the enclosing adventitial tissues (Fig. 1.27).

LYMPH NODE. The magnitude of radiation effect varies according to the relative anatomic position with regard to directional and intensity factors. Without exception, however, there has been a severe depletion of the small lymphocyte population (Fig. 1.28). This produces in the lymph node a loose reticular pattern in which the capsule and the trabeculations are more prominent than usual. The residua of the medullary cords are difficult to

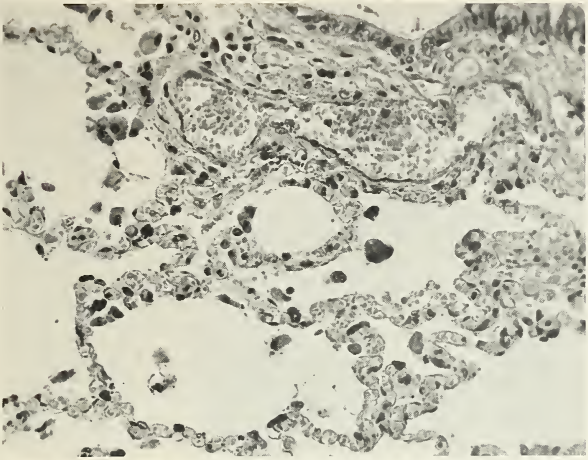


Fig. 1.20 Lung. Essentially normal respiratory parenchyma.

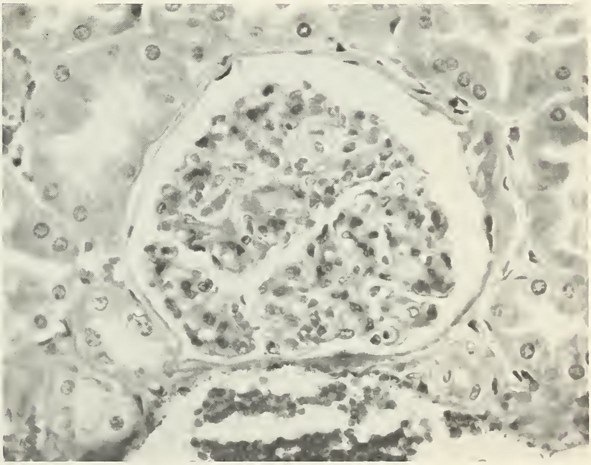


Fig. 1.21 Kidney. Minimal epithelial and endothelial swelling.

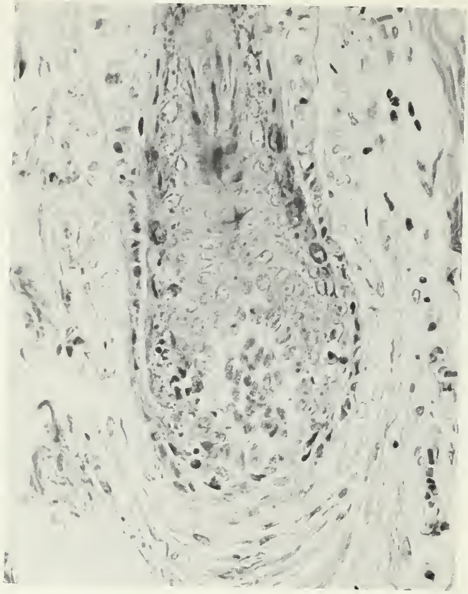


Fig. 1.22 Hair follicle. Pyknotic and fragmenting hair matrix cells.

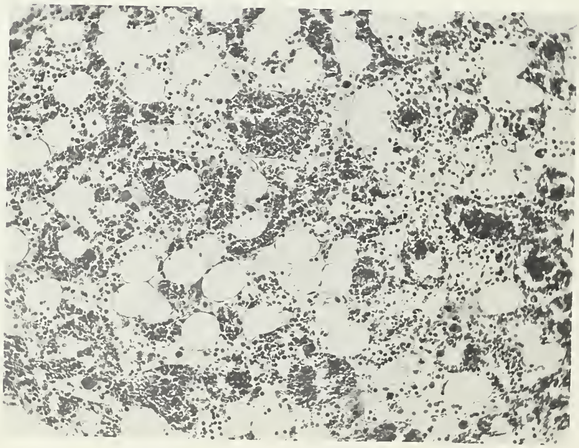


Fig. 1.23 Bone marrow. Marked reduction of hematopoietic cells.

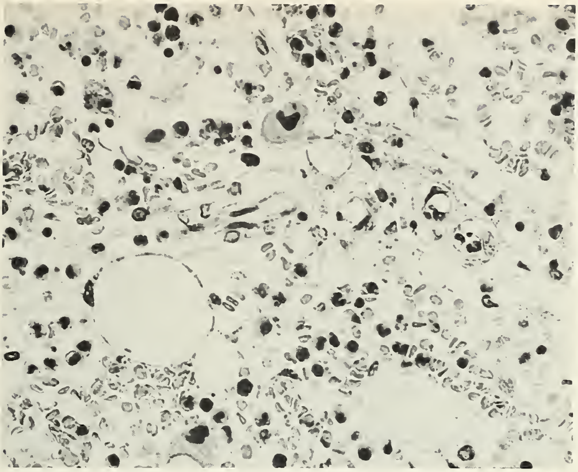


Fig. 1.24 Bone marrow. Early microvascular effects.

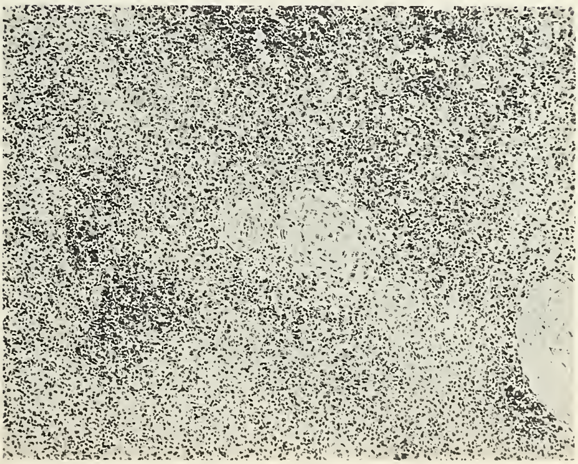


Fig. 1.25 Spleen. Depletion of lymphocytes and collapse of sinusoids.

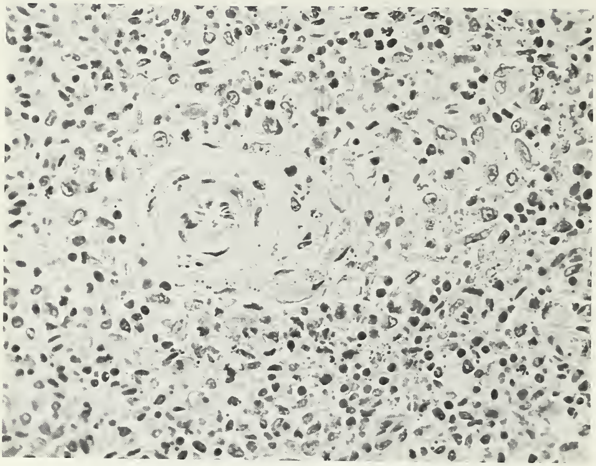


Fig. 1.26 Spleen. Loss of white pulp definition.

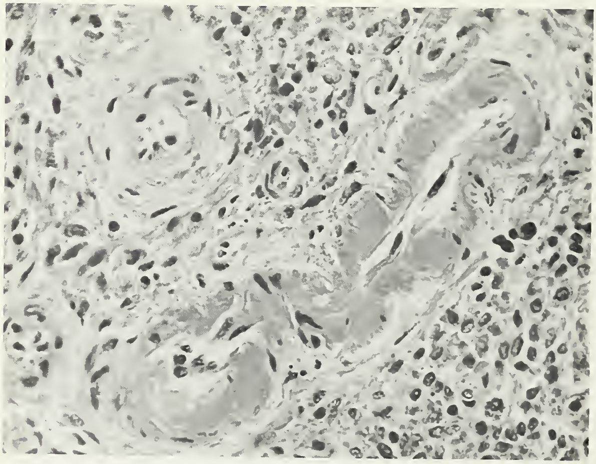


Fig. 1.27 Spleen. Thickened sheathed arteries.

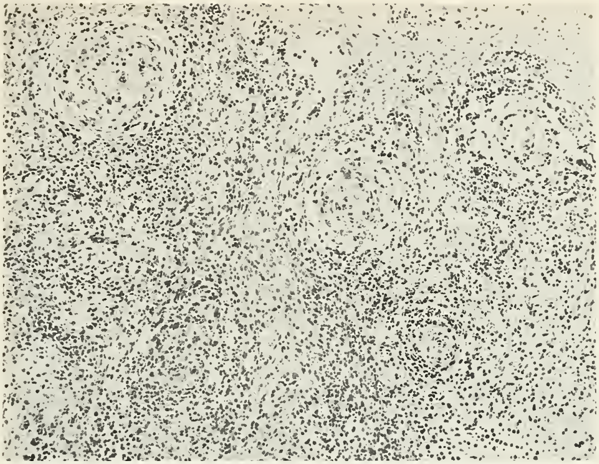


Fig. 1.28 Lymph node. Residua of peripheral germinal nodules.

identify because of the depletion of normal cellularity. At the periphery of the nodes are the remnants of the lymphatic nodules seen now to be composed largely of irregularly and concentrically arranged reticular and connective-tissue cells (Fig. 1.29). There is a transition of many of these cells to macrophagic function with the presence within these swollen cells of large quantities of nuclear and cytoplasmic debris (Fig. 1.30). Viable and functional lymphocytes for practical consideration are virtually absent. There is a diffuse but rather slight infiltration of both cortical and medullary areas by granulocytes.

INTESTINE. Moderately advanced autolysis of the mucosa is a problem in attempting to evaluate the histopathology of this case. Although many of the crypts remain intact, much of the epithelial lining of the villi has been denuded, and interpretations must be based upon the residual strips. From what may be observed, the tissue changes differ only slightly from those noted in case A (905226). The principal features are a decrease in total crypt-cell population, moderate pleomorphism of the principal cells in the proliferative and maturation zones of the crypts, in situ development of capacity for mucin production, suppression of mitosis, and progression of pleomorphic cells up through the neck and to the bases of the villi. The lining cells of the villi are for the most part uniform in morphology. There is a tendency toward piling up of mature cells at the points of extrusion at the tips of the villi. Active cell degeneration in the epithelium is minimal. The Paneth's cells remain essentially unaltered. The lamina propria and submucosa exhibit a relative hypocellularity with a variable slight infiltrate of granulocytes, plasma cells, and monocytes. The small vessels in the submucosa display endothelial swelling as well as swelling of the nuclei and cytoplasm of the smooth-muscle elements in their walls.

STOMACH. The autolytic changes, even though of moderate degree, preclude any accurate interpretation of possible early injury incurred through the actions of ionizing radiation. Cells in the neck regions of the gastric glands show enlargement and nuclear pyknosis along with some that are binucleate.

ESOPHAGUS. The only histological changes present that would indicate a possible relationship to the irradiation is a lack of mitotic activity along the basal-cell layer of the mucosal epithelium and swelling of the smooth-muscle cells in some of the arterioles of the submucosa.

LIVER. There is a variable degree of amorphous degenerative change in the walls of arterioles in the portal triad areas. There is no significant change in the ductal epithelium or in the hepatic cell parenchyma.

PANCREAS. The intercession of autolytic changes affecting portions of the pancreas makes identification and interpretation of possible other histopathology exceedingly difficult. Over and above this terminal process, however, there appear to be small and scattered foci of acinar-cell degeneration characterized by excessive cytoplasmic vacuolation and granularity, and nuclear pyknosis and karyorrhexis. In these areas, there is a slight infiltrate of granulocytic cells which would seem to indicate a process unrelated to autolysis or terminal change. The etiology of this focal pancreatitis is obscure, and there is no apparent vascular or ductal pathology that might be considered contributory. The islands of Langerhans do not show any significant cellular pathology.

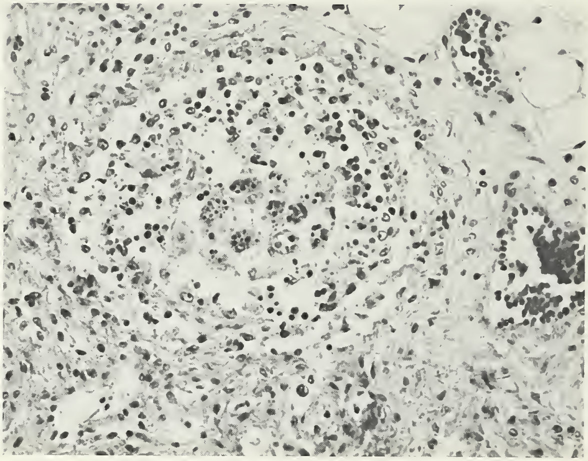


Fig. 1.29 Lymph node. Marked depletion of small lymphocytes.

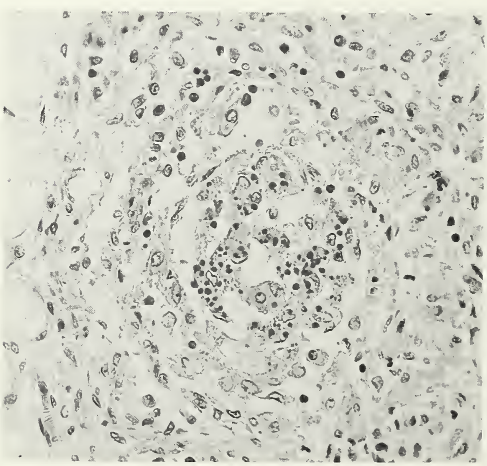


Fig. 1.30 Lymph node. Phagocytosis of debris from nodule.

BRAIN. No lesions of any major significance are identified by light microscopy of numerous sections throughout the various portions of the brain and brain stem. The most obvious finding is a clear halo about the blood vessels indicating a separation of the brain parenchyma from the vessel walls. Although some of this may be artifact, it would appear that there is evidence indicating the probable extravasation of fluid through the vessel wall thereby forcing away the adjacent parenchyma. Changes are observed in the microvasculature, but these are scattered, inconsistent, and variable in degree. The principal feature is focal amorphous and fibrinoid thickening in the intimal and subintimal strata and occasionally a slight swelling of the individual smooth-muscle cells. Rarely, a slight perivascular extravasation of erythrocytes may be noted. Deep in some of the sulci aggregates of granulocytes are seen with no discernible reason for their presence. Scattered randomly throughout the brain substance are very small and irregular foci of spongy demyelination with no associated glial response. The nerve cells throughout all sections fail to show any relevant cytopathology.

TESTIS. Some widening of the interstitial spaces between the tubules indicates likelihood of edema. The structure of the tubules is not markedly altered although the depth of the germinative epithelium is diminished by about one-quarter to one-third that of normal and there are large numbers of degenerating spermatogenic cells within the lumens (Fig. 1.31). Although in most areas there is early degeneration of a considerable portion of the spermatogenic cells, there are other areas where all cell stages can be identified and where most of the cell components do not exhibit any overt morphologic change (Fig. 1.32). As in case A, the mature spermatozoa, although decreased in total number, and the Sertoli cells aligned along the base of the epithelium show no pathology. The interstitial cells are unremarkable, and the vessels show much the same change observed in case A.

HEART. The overall histologic structure of the heart is unremarkable. Certain features, however, bear careful consideration in light of the findings in the previous case (905226). Some similarities exist which cannot be overlooked. There are multiple scattered small foci of extravasated red blood cells. For the most part these are associated with minimal dissection between essentially normal-appearing cardiac muscle bundles. In a few instances, particularly in the papillary muscles, these foci are larger, and the extravasation takes on more of the characteristics of a true microhemorrhage with some concomitant disruption of muscle fibers and a limited infiltration by mononuclear cells and segmented granulocytes. Especially in these areas, but also throughout the heart, many of the small arterioles display what appears to be a segmental necrotizing vasculitis (Fig. 1.33). There is vacuolation of the smooth-muscle cells alternating with a smudgy amorphous decomposition giving the appearance of a very fragile and discontinuous vascular channel. There are, in fact, aggregates of leukocytes localized in these areas. Some of the microvessels of the epicardial adipose tissue exhibit similar findings, indicating that this process is not specific for the myocardium. The cardiac muscle fibers themselves show little evidence of any sort of discontinuity or degeneration except for some areas near the bases of the papillary muscles where there are interdigitating bands of fibrous tissue consistent with an ischemic change of some long standing. The lumens of the small arteries in these areas are narrowed by a fibrotic thickening of the walls which has no relationship to the radiation injury.

LUNGS. There are areas of atelectasis alternating with acute compensatory emphysematous expansion of alveoli. Throughout the parenchyma there is moderate dilation and congestion of the vascular channels and a diffuse edema, evidences of which may be seen in almost every section examined. In most areas the alveoli contain large numbers of macrophages swollen by vacuoles, organic debris, and pigment granules as well as relatively small numbers of monocytes and granulocytes. There is also apparent a rather diffuse reaction on the part of the alveolar lining cells and the septal cells as evidenced by certain variable enlargement of these cells, some of which are already showing phagocytic properties. Evidence of direct radiation effect is in no way convincing, although many of the arterioles show a slight discontinuous hyalin-like thickening in the subendothelial and intimal areas and some vacuolation of the smooth-muscle cells. The same features are prominent in many other tissues of this case (Fig. 1.34).

KIDNEY. There is no disturbance in the overall histologic structure of the kidney. The glomeruli are numerous and of normal cellularity. There is no broadening of the interstitial spaces between the tubules. The epithelial cells of the convoluted tubules are somewhat swollen, and their inner borders are irregular and indistinct. The cytoplasm is finely granular with an occasional vacuole. The nuclei are uniformly ovoid or spherical in configuration. Some appear smaller than others and have a homogeneity to the nuclear substance which is not considered normal but is often seen as a terminal or postmortem change. The same etiology can be applied to the similar cytoplasmic changes. There appears to be a variable degree of fibrinous thickening in the subendothelial zone of the glomerular loops along with occasional vacuolation within the endothelial cells (Fig. 1.35). A few of the glomerular epithelial cells also show some degree of enlargement; however, these changes are rather inconsistent. The capsular epithelium is normal, and there is no appreciable thickening of Bowman's capsule. In the arteries and small arterioles, especially the afferent arterioles, there is an occasional focal area of subintimal hyalinosis but without appreciable constriction of the vessel lumen. The changes seen in the kidney, therefore, coincide with the vascular alterations noted elsewhere in the body. The tubule epithelial changes are equivocal and probably the result of terminal or postmortem degenerative change.

URINARY BLADDER. The degree of autolytic slough of the epithelium precludes any accurate evaluation of the effect of radiation upon the epithelium. Those cells which remain show minimal pleomorphism and no mitotic activity. The submucosal tissues have only slight edema along with some dilation and congestion of the vessels. An occasional small submucosal hemorrhage is noted.

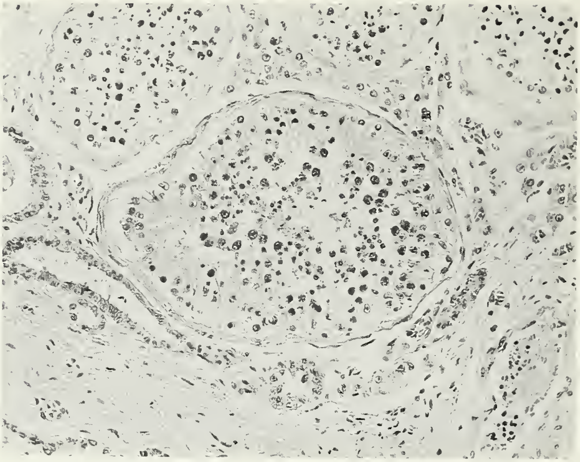


Fig. 1.31 Testis. Tubule lumens filled with spermatogenic cell debris.

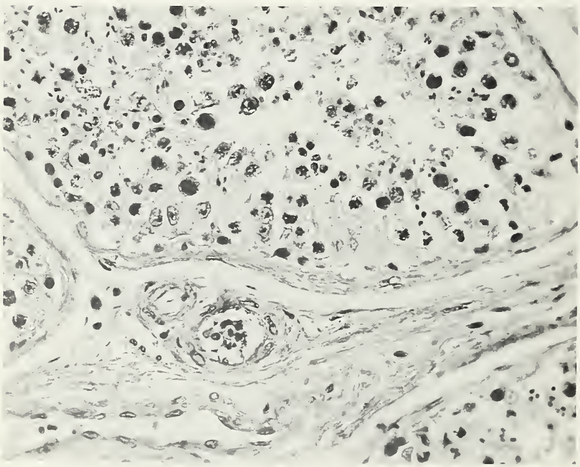


Fig. 1.32 Testis. Degenerative changes in spermatogonia and spermatocytes.

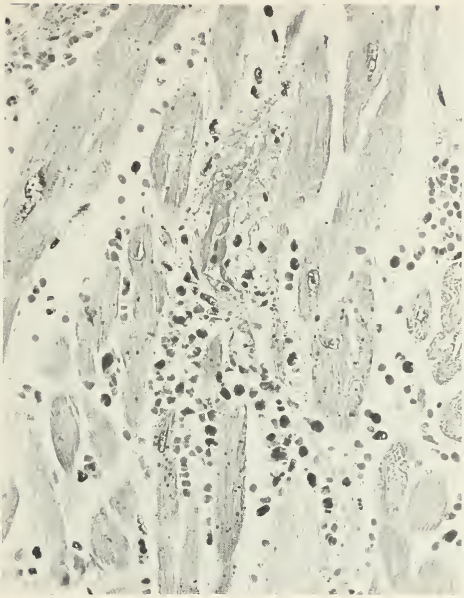


Fig. 1.33 Heart. Segmental vasculitis with microhemorrhage.

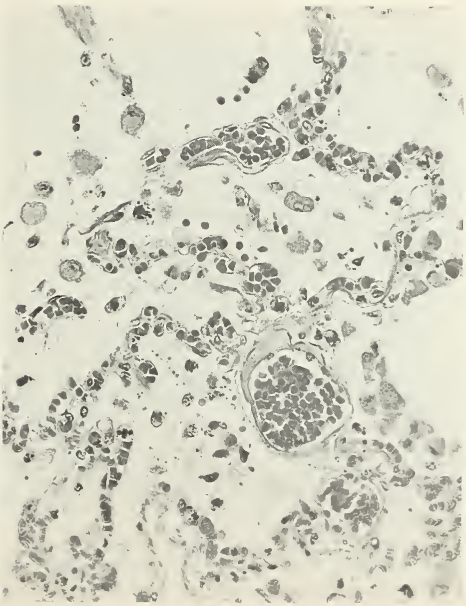


Fig. 1.34 Lung. Early microvascular effects.

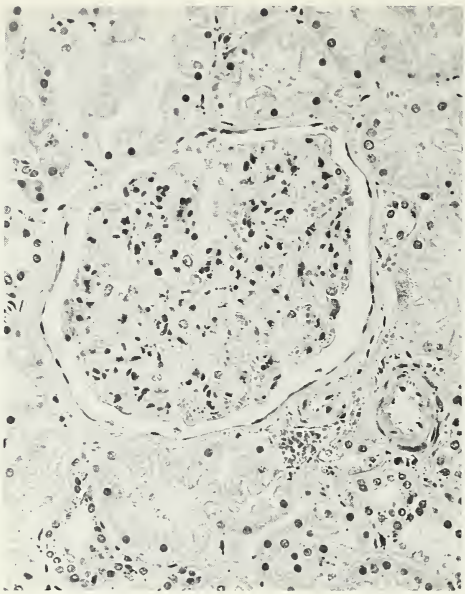


Fig. 1.35 Kidney. Early glomerular changes.

Case C (1147724)

BONE MARROW. For all practical considerations, the marrow is totally devoid of hematopoietic constituents (Fig. 1.36). The histology is that of a field of fat cells traversed by dilated and congested sinusoids and broad interlacing bands of a very loose, reticular matrix appearing to be composed largely of an amorphous protein-rich substance with meshes of fibrin. Other than the fat cells and the lining cells of the sinusoids, few nucleated components remain. Of these, the reticular cells, many of which show distinctive stellate cytoplasmic processes, and plasma cells are the most numerous (Fig. 1.37). A few segmented granulocytic cells are identified as well as an occasional atypical megakaryocyte. No cells are identifiable as hematopoietic progenitor cells. If primitive stem cells are indeed present, then they may be morphologically similar to the reticular cells.

SPLEEN. The overall histology is uniform and characterized by pronounced hypocellularity. The red pulp is unusually prominent in that the sinusoids are dilated and congested with erythrocytes (Fig. 1.38). The fibrous trabeculations and the sheathed arteries and arterioles obtain a relative prominence owing to the depletion of the lymphoid component and compaction of the remaining splenic parenchyma. At high magnification it is evident that the only significant localization of nucleated elements is in the residual white pulp areas about the arterioles, and it is in these depleted meshes of reticular cells and connective tissue that there is a sparse cell population of largely indeterminate ancestry (Fig. 1.39). The largest of these cell forms, which exceed in diameter the readily identifiable reticulum cells, are irregularly spherical in configuration, have prominent hyperchromatic nuclei containing one to three large nucleoli, and exhibit some margination of the condensed nuclear chromatin. Some of these cells have a few fine granules in the cytoplasm, and some are attempting cell division. More often than not these mitotic figures are atypical. In addition, a larger population of medium-sized mononuclear cells also exhibits some cell division, but the nuclei do not show the same prominent nucleoli or the exaggerated condensation of the chromatin. Although most of the nuclei of these medium-sized cells are ovoid or spherical, a few display distinct folds or indentations. The cytoplasm is homogeneous or finely granular. Many of the aforementioned large- and medium-sized cells have morphologic characteristics suggestive of the lymphocytic or monocytic series. Added to the reticulum cells and to the large- and medium-sized mononuclear cells are readily defined plasma cells and a few granulocytes and small lymphocytes. Also, numerous pyknotic and karyorrhectic cells appear to be the degenerating products of abnormal cell divisions. Macrophages are active though not unusually abundant throughout this white pulp area, and they contain nuclear debris, erythrocytes, and vacuoles. The sheathed arteries are distinctly prominent. Among the factors con-

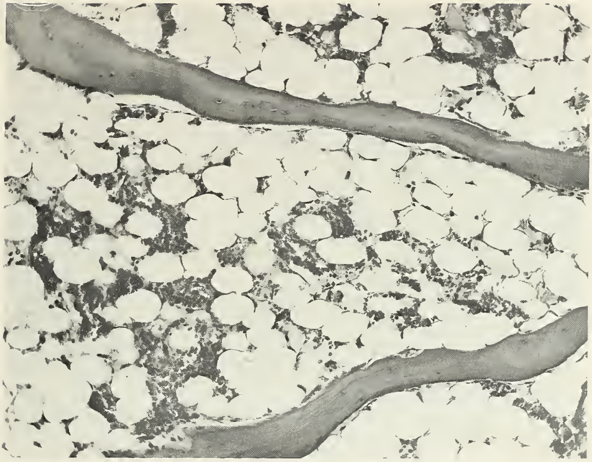


Fig. 1.36 Bone marrow. Total depletion of hematopoietic elements.

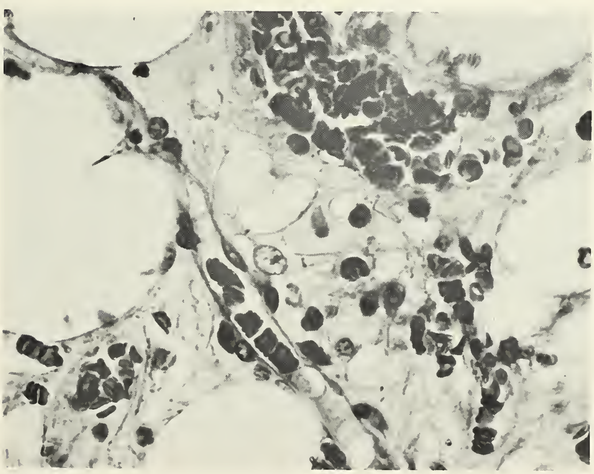


Fig. 1.37 Bone marrow. No identifiable residual hematopoietic cells.

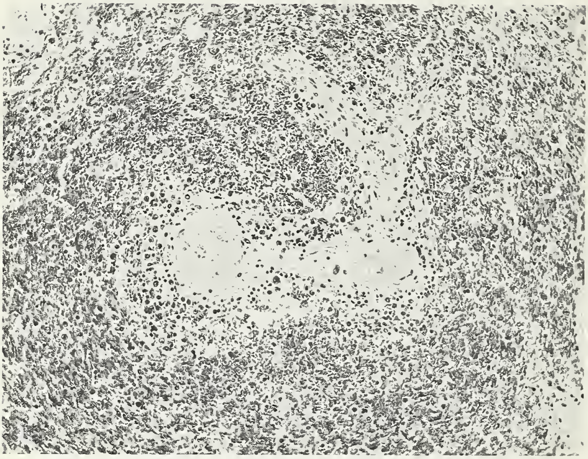


Fig. 1.38 Spleen. Congestion and pronounced white pulp hypocellularity.

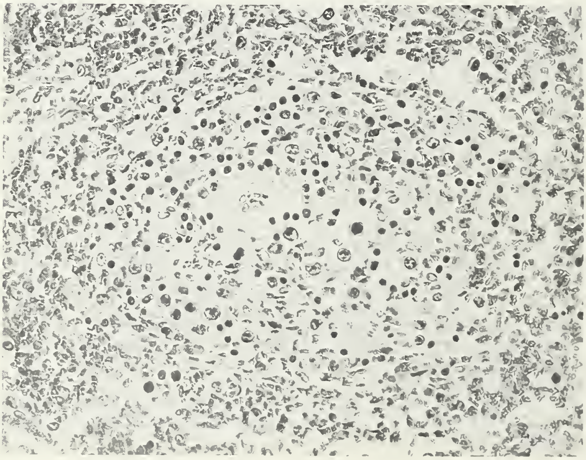


Fig. 1.39 Spleen. Appearance of atypical mononuclear cells.

tributing to this are swelling and vacuolation of the endothelial cells; focal subintimal deposition of a densely eosinophilic homogeneous material, which is observed to be distributed unevenly and randomly along the lengths of these arteries (Fig. 1.40); variable swelling, vacuolation, and degeneration of the smooth-muscle cells; and a loose fenestration of the adventitia within which may be seen occasional small mononuclear cells and granulocytes. These processes acting together seldom occlude the vessel but do serve to markedly constrict its lumen.

LYMPH NODE. The majority of the lymph nodes exhibit a dramatic depletion of the lymphocyte population. The medullary cords and the peripheral lymphoid nodules are dominated by cell types that would under normal circumstances have been relatively obscure by virtue of the usual abundance of small lymphocytes (Fig. 1.41). A few large lymphocytes show some cytoplasmic vacuolation and irregularity of nuclear outline. Large monocytic cells show deep infolding of the hyperchromatic nuclei, and reticular cells and plasma cells are relatively abundant. The infrequent small lymphocytes, however, exhibit marked chromatin condensation, compaction of the nucleus, and, in some instances, nuclear fragmentation. The sinusoidal areas are congested, if not actually hemorrhagic, and contain numerous histiocytes and mononuclear cells. Mitotic figures are scarce and are seen only in cells having morphologic characteristics relating to the medium or large lymphocyte categories.

THYMUS. A few small vestiges of thymic tissue are embedded in a sea of fat cells. The majority of the cells of this tissue are of the epithelioid type of thymic cell. Hassal's bodies are identified, and most of these are cystic and contain keratin debris, some of which has become calcified. There are a few aggregates of small thymocytes, some of which are distinctly pyknotic, with others showing nuclear fragmentation. There is no evidence of any attempted regeneration of this particular cell population.

INTESTINE. In contrast to the basically normal appearance of the sections from cases A and B, the mucosa of the small intestine in this individual has been drastically altered (Fig. 1.42). The villi vary markedly in height, breadth, and configuration, ranging from very foreshortened and poorly defined nubbins to structures about two-thirds normal height showing varying degrees of edema, vascular congestion and hemorrhage. There has been almost total denudation of the mucosa; much of this is a direct effect of radiation with the superimposition of autolysis. Almost all identifiable residual epithelial cells are situated in the regions of the crypts or near the bases of the poorly delineated villi (Fig. 1.43). These cells are in varying conditions of degeneration; many are large and bizarre with pleomorphic nuclei, some are beginning to show a diffuse homogeneity to the nucleus and cytoplasm, and still others exhibit pyknosis and nuclear fragmentation. Occasional residual Paneth's cells can be identified at the extreme bases of the crypts, and their eosinophilic granules are few and of variable size. Many of these crypts have assumed microcystic configurations lined by distorted cells and containing debris. Occasional intracellular processes resembling attempted and abortive mitoses are identified; however, these are very abnormal in composition. In addition to edema and hemorrhage of the lamina propria and submucosal tissues, large numbers of plasma cells are present along with a scattering of small, poorly defined pyknotic cells, which may be of lymphatic or granulocytic derivation. Colonies of bacteria are present on the mucosal surface with some aggregates of bacilli seen deep in the crypt areas.

STOMACH. The overall pattern of the mucosa is within normal limits. The surface epithelium and the epithelium lining the gastric pits consist of uniform, well-differentiated, tall columnar cells having an abundance of cytoplasmic mucin. In the gastric glands there is some loss of cohesion of the epithelial cells, which may be due to early autolysis. On the other hand, some of these cells, both zymogenic and parietal, show multinucleation and large and bizarre nuclei (Fig. 1.44). As the deeper reaches of the gastric glands are examined, these early degenerative changes are somewhat less conspicuous, with the zymogen and parietal cells having essentially normal morphology. Mitotic figures are infrequent although most appear normal. There is dilation and congestion of the superficial vessels.

LIVER. With the exception of a variable swelling of the smooth-muscle cells in the arteries of the portal triads, there is no histologic change of any significance.

GALL BLADDER. The epithelium lining the gall bladder appears to be relatively resistant to ionizing radiation. Although there is a moderate to severe degree of autolytic epithelial denudation, those portions of the epithelium remaining in situ show uniformity of the tall columnar cells. There is no evidence of nuclear or cytoplasmic change relative to radiation.

PANCREAS. The normal architecture is preserved. There is no depletion of the islands of Langerhans, and the cellular components of these structures appear to be of normal morphology. In general, it might be said that the acinar cells are somewhat smaller than usual, which may be due to a relative depletion in most of the cells of the number of zymogen granules. Although a slight amount of nuclear pleomorphism exists, evidence of any widespread early parenchymal cell degeneration is not evidenced. In the interstitial tissues, some of the small arteries show the same subintimal hyalin material as seen in the vessels of other tissues of the body.

TESTIS. The average diameter of the seminiferous tubules is reduced by one-third to one-half. There is some broadening of the interstitial areas, most of which seems to be the result of an accumulation of edema (Fig. 1.45). There is no visual evidence of a change in the population of interstitial Leydig cells, and there is not any associated cytopathology. Many of the arterioles exhibit a moderate degree of prominence of the endothelial nuclei, and there is some swelling of the smooth-muscle cells. The principal change has taken place in the germinative epithelium of the tubules. The variegated histologic pattern confirms the wavelike kinetics of spermatogenesis along the length of the tubule. Even in the same cross-section of a single tubule, the picture may range from a greatly reduced epithelium

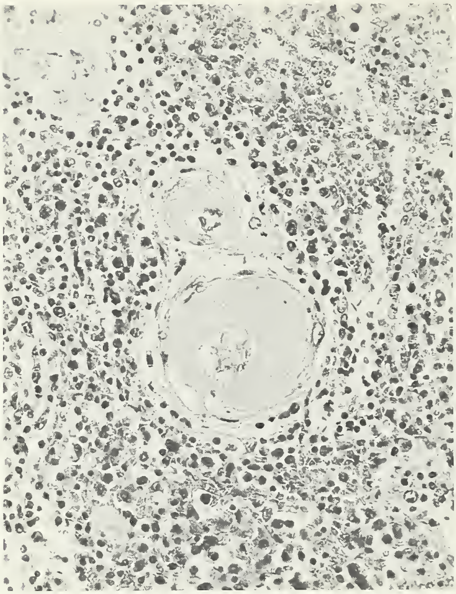


Fig. 1.40 Spleen. Hyaline thickness of arteries.

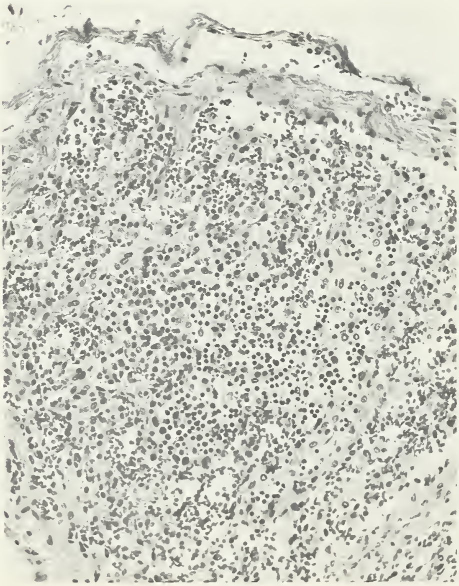


Fig. 1.41 Lymph node. Early lymphocyte regenerative efforts.

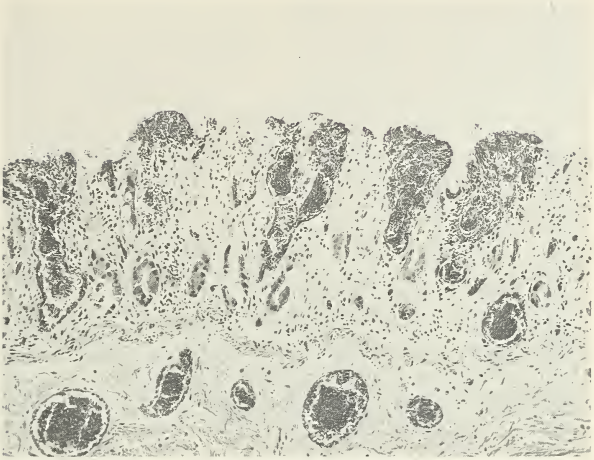


Fig. 1.42 Intestine. Mucosal edema, congestion, and epithelial denudation.

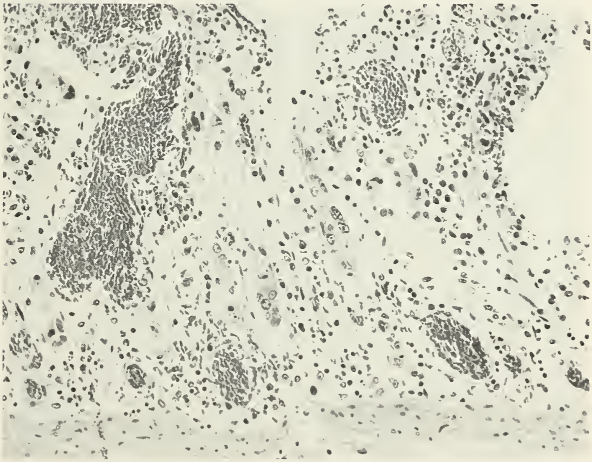


Fig. 1.43 Intestine. Residual epithelium is pleomorphic.

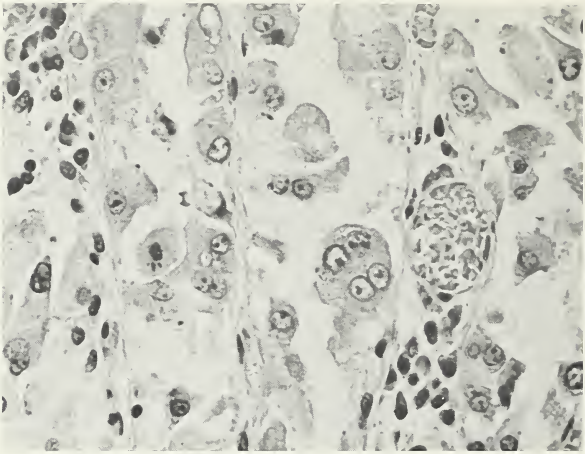


Fig. 1.44 Stomach. Epithelial cell pleomorphism and multinucleation.

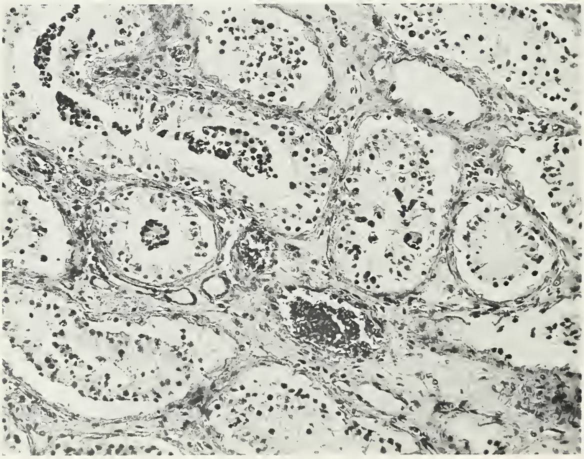


Fig. 1.45 Testis. Cellularity of spermatogenic epithelium greatly diminished.

consisting almost entirely of Sertoli cells to a greater depth of epithelium exhibiting several states of residual spermatogenesis. In terms of the overall histopathology, there is a dearth of spermatogonia in the deepest zone of the epithelium, with a relative prominence of Sertoli cells (Fig. 1.46). These latter cells are palisaded along the basement membrane. Because of the relative lack of spermatogonia, the nuclei of these Sertoli cells have come to occupy a parabasal position, with the cytoplasm polarized perpendicular to the basement membrane and the distal ends of the cytoplasm streaming into the lumen with rather poorly defined cell borders. The Sertoli cell nuclei are uniformly ovoid with a few showing slight indentations or infolding. Interspersed along the basement membrane among the bases of the Sertoli cells are spherical or ovoid cells presumed to be residual spermatogonia of the more radioresistant form on the basis of position and morphology. The nuclei are rounded with the nuclear substance slightly granular to homogeneous. The cytoplasm is of moderate amount and is finely granular. The luminal two-thirds of the seminiferous epithelium is occupied primarily by residual spermatocytes and spermatids, the majority of which are undergoing degenerative changes although some still exhibit the cytological characteristics of normal spermatogenic transformations. By light microscopy it is difficult to define specific defects that might be responsible for the initiation of cell degeneration, but the various overt stages of cell destruction are in evidence. In the spermatocytes there is an abnormal cohesion of the filamentous chromatin with an irregular clumping of these strands. Often there appear clear voids or vesicles in the nuclei between these clumps of chromatin. The meiotic divisions appear to be abortive, and, although nuclear division may occur, it is apparent that cytoplasmic separation often fails. Multiple nuclear fragments, karyomeres, are seen in the daughter cells, and the nuclei are condensed and often fragmented. The postmeiotic spermatids are diminished in overall number in essentially the same proportion as are the spermatocytes. Because of the smaller unit size of this phase of spermatogenic maturation, definitive cytopathology is not readily distinguished by light microscopy. Mature sperm are very few in number presumably owing to the completion of their maturation and subsequent expulsion. The lumens now contain plugs of compacted degenerating cells and cellular debris, sometimes to the extent of occluding the tubule lumen. These cells are predominantly degenerating spermatocytes and spermatids. In some lumens there are large and bizarre cell forms. Not infrequently, degenerating cells have coalesced into rosette patterns and appear in the lumens as multinucleated giant cells.

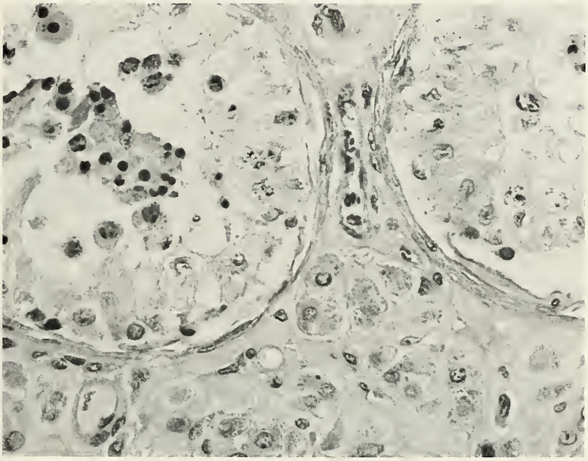


Fig. 1.46 Testis. Predominance of Sertoli cells lining tubules.

HEART. The cardiac histology does not deviate significantly from the norm, with the exception of the small nutrient arterioles, which show some of the changes already observed in the other instances of lethal whole-body irradiation, and also seen elsewhere in this same case. There is some crowding together of the endothelial nuclei, and these frequently have a rounded configuration. There is an ill-defined fenestration of the subintimal zone and muscle layers with foci of fibrinoid degeneration. Whether this represents a direct response to the radiation or whether this is a change that is consistent with the overall clinical condition or medical management cannot be stated with

any assurance. There are a few small, very recent interstitial hemorrhages that could well be terminal and not directly related to the irradiation.

LUNGS. Multiple sections through the lungs reveal no histologic changes relevant to the absorption of ionizing radiation. In contrast to the vessels in other portions of the body, the small arteries of the pulmonary parenchyma do not present any significant endothelial swelling or any deposition of hyalin material in the subintimal or subendothelial zones. The lining epithelium of the bronchioles is of a uniform, ciliated columnar type with the nuclei displaying a minimal degree of pleomorphism, which is compatible with normal variation. The septa are thin and interlacing with no swelling of the septal cells or alveolar lining cells.

KIDNEYS. The renal parenchyma is remarkably free of any histopathology that might be considered related to the response to radiation. An occasional arteriole shows a small area of smudginess in the medial portion, or a slight focal fenestration, but these are spotty in occurrence and are of questionable significance.

BLADDER. This structure is also unremarkable in its histologic appearance. The lining epithelium is of a uniform transitional type. The only feature that suggests the possibility of radiation response is that in a few focal areas there are aggregates of epithelial cells at the extrusion zone of the epithelium. These cells are large and pleomorphic with bizarre nuclei. This feature, however, is not uncommonly seen even under normal circumstances.

SKIN. Sections through the skin taken from a marginal area of intense radiation exposure disclose the primary histopathology to be in the epidermis and its contiguous structures, specifically the hair follicles. The overall depth of the epidermis has been only slightly decreased. Of primary interest is the pronounced deficit in the population of the basal-cell layer (Fig. 1.47). Although there are numerous cells surmounting the basement membrane whose polarity and general morphology resemble the basal-cell type, there is disparity of size and moderate pleomorphism. Among these cells, there is cytoplasmic vacuolation, irregular condensation of nuclear chromatin, and, in many instances, poor cohesion to the basement membrane, such that there are areas of distinct separation not considered to be artifact (Fig. 1.48). There are in fact focal areas along this basal zone where there are no nucleated elements at all or where there are only ghostlike remnants of these altered cells. No evidence of mitotic activity is displayed, and this loss of regenerative capacity is reflected in the overall decrease of nucleated cells throughout the thickness of the epidermis. Delineation of the remaining epidermal cells is poor, and large areas have indistinct or obliterated intercellular bridging. Nuclear pleomorphism is moderate throughout the stratum Malpighii, and there are focal areas where there is more advanced and extensive cell degeneration heralding impending ulceration. The epidermis is surmounted by a fenestrated zone of cornified cells. Similar cytopathology is observed along the sheath of the hair follicles, with total deletion of the generative portion of the follicle and destruction of the normal inner matrix. The principal cells of the sebaceous glands and the sweat glands disclose little change. The nuclei are uniform in size and configuration, although the cells themselves do show slight variation in size. There is only occasional cytoplasmic vacuolation in the epithelium of the sweat glands. On the other hand, there is distinctly more distortion and cell degeneration in the epithelial cells of the ducts associated with these glands. There is a rather unimpressive degree of nuclear enlargement and cellular vacuolation in the endothelium and smooth-muscle cells of the arterioles lying within the dermis. The collagen fibers and connective-tissue cells that form the bulk of the dermal tissue do not show any significant histopathologic change.

Case D (1147723)

BONE MARROW. The marrow has reformed a portion of its depleted hematopoietic compartment with the overall cellularity reconstituted to about one-third to one-half normal (Fig. 1.49). The regenerating population is spread diffusely throughout the marrow although there is some tendency toward focalization, and, in many instances, these nidi appear most conspicuous about the marrow vessels (Fig. 1.50). Classification of the individual cells is difficult primarily because many are abnormal progeny of inadequate, incomplete, or otherwise abnormal cell divisions. It is apparent, however, that they represent maturation stages of both the myelocytic and erythrocytic series with a few more primitive forms of these series also in evidence. Mitotic figures are relatively numerous though frequently atypical. Megakaryoblasts may be identified among the larger cell forms, and some of these already show a degree of differentiation and multinucleation. There is still an unusually high ratio of plasma cells and monocytes along with an increasing small lymphocyte component. In many instances, the plasma cells are observed to be localized along the marrow vessels.

SPLEEN. The red pulp is particularly prominent because of an intense congestion of the sinusoids. There is no associated infiltrate of reactive cells above and beyond those normally present in this area. The white pulp is once again beginning to form about the sheathed arteries, although at this phase of recovery the volume is still only about one-third that of normal (Fig. 1.51). Small lymphocytes appear to predominate; however, many show nuclear atypism and even binucleation. Some of these lymphocytes also continue to exhibit more advanced degenerative changes. Many larger cell forms are present whose nuclear and cytoplasmic characteristics strongly suggest a lymphocytic lineage (Fig. 1.52). Many of these cells, however, display pleomorphism of the nuclei with abnormal chromatin clumping and the presence of karyomeres in the adjacent cytoplasm. Many are attempting division; a large proportion of these mitotic figures are of abnormal structure. Monocytes and plasma cells abound but do not enjoy the dominant role observed at the prior stage of peak cellular depletion. The sheathed arteries exhibit an exaggerated hyalinosis of the intima and subintima zones along with some degree of enlargement of the endothelial cells and vacuolation of these cells and the smooth-muscle cells of the media. In some of these arteries, there are distinctive focal anuclear fibrinoid areas of the vessel wall.

Fig. 1.47 Skin. Early epidermal disorganization and relative hypocellularity.

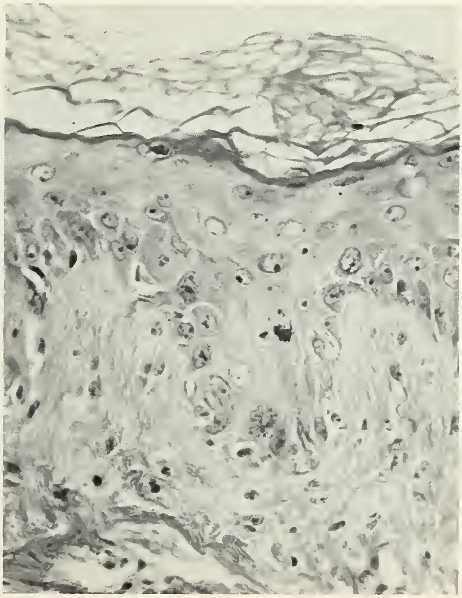


Fig. 1.48 Skin. Basal layer depopulation and loss of cohesion.

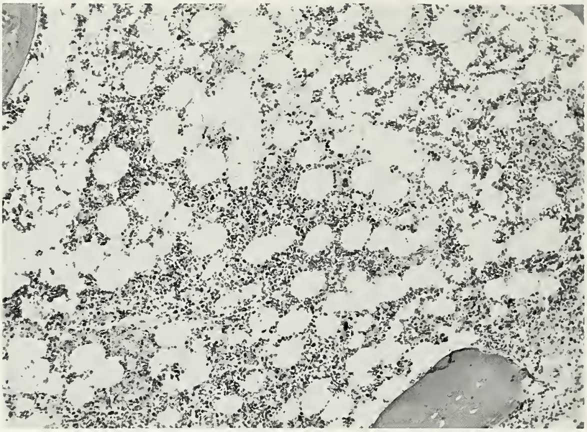


Fig. 1.49 Bone marrow. Early hematopoietic regeneration.

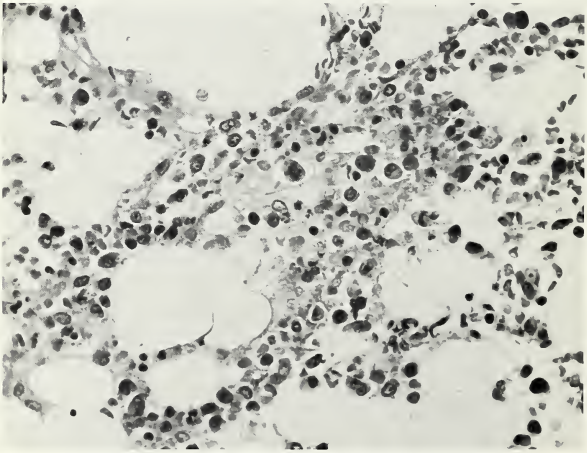


Fig. 1.50 Bone marrow. Many newly formed cells are abnormal.

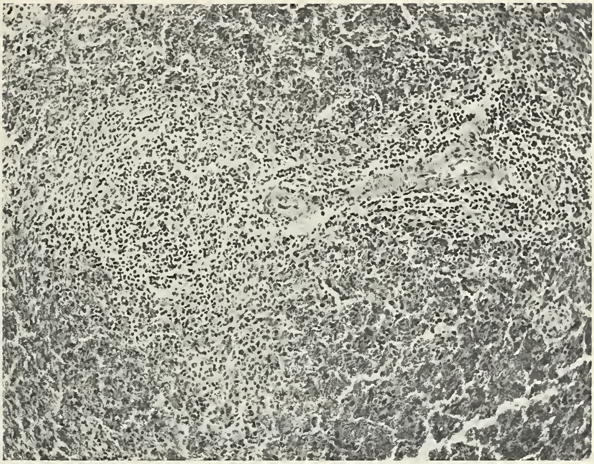


Fig. 1.51 Spleen. Reconstruction of white pulp.

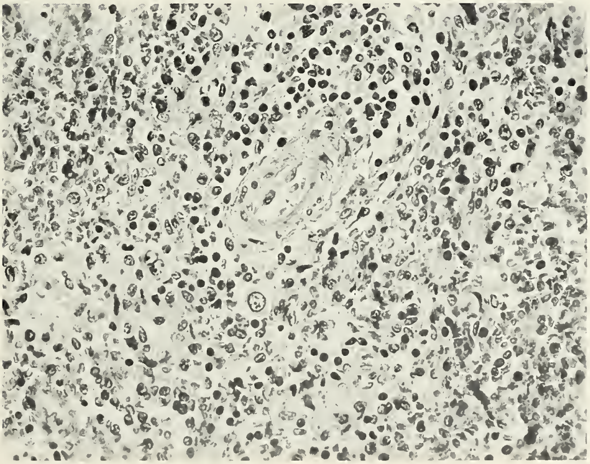


Fig. 1.52 Spleen. Many large, abnormal cells typifying the regenerating white pulp.

LYMPH NODE. The medullary cords have reconstituted much of their preexposure population although there is little evidence of any reformation of germinal centers near the periphery of the node. These medullary cords and the clusters of cells near the periphery are composed of a variety of cell types (Fig. 1.53). Cells of the lymphocytic series dominate the population with a relative abundance of small lymphocytes, many of which show an atypical configuration to the nucleus or binucleation. Medium lymphocytes and some large lymphocytes are present, and there are mitotic figures seeming to represent cell divisions in these clusters of potentially proliferative lymphocytic cells. There are, in addition, even larger cell forms having abundant cytoplasm and large, irregular nuclei with clumping of the nuclear chromatin. These cells do not readily fall into any specific category and have the appearance of being distorted macrocellular forms of abnormal generative cycles. Plasma cells and some granulocytes are also in evidence.

THYMUS. The atrophic thymic tissue consists of multiple small, isolated stellate foci consisting almost entirely of the epithelioid form of thymocyte with embedded cystic structures containing whorls of keratin debris. The degree of involution of this gland precludes any evaluation of radiation response.

INTESTINE. On the basis of the material at hand for this particular case, it is very difficult to evaluate the full extent of the damage to the intestinal mucosa. There is all but total eradication of the normal villous pattern, emphasized by a regression in the depth of the mucosa to about one-half of normal (Fig. 1.54). For that matter, in some areas there is a complete slough of the mucosa with superficial ulceration into the submucosa. Much of the mucosa is now a disorganized reticular network containing macrophages, plasma cells, and monocytes. There are infrequent blunted glandular structures of a regenerative form. The epithelium is tall, columnar, and densely staining with the nuclei uniformly ovoid and slightly hyperchromatic. Mitotic figures in these scattered reforming glands are relatively numerous. Occasional debris-filled cystic remnants of intestinal glands are identified, and these are lined by flattened and pleomorphic epithelial cells. There is condensation of the submucosal connective tissue, and some of the fibroblasts already are enlarged and pleomorphic, presenting characteristics identified with the radiation fibroblast. Vascular changes are present but are variable and not particularly noteworthy.

LIVER. There are no changes within the liver parenchyma or its supportive elements suggestive of a specific response to radiation.

PANCREAS. There are no significant changes noted in either the acinar cells or in the cells of the islets of Langerhans.

TESTIS. Although there is no disruption of the overall structure of the testicular parenchyma, there is a dramatic change in the seminiferous tubules. They are markedly atrophic and reduced in size to about one-half to two-thirds normal diameter (Fig. 1.55). The interstitial tissues have not yet condensed to accommodate the tubular atrophy; consequently, there is a loose edematous appearance to this supportive component. Instead of the normal variegated cellular pattern of spermatogenesis, the lining of the tubules consists of palisaded, radially polarized Sertoli cells whose wispy, ill-defined luminal processes project into the mostly empty tubular lumens (Fig. 1.56). The parabasally situated nuclei of these Sertoli cells are uniformly ovoid. Of particular interest are the sparse, randomly interspersed smaller rounded cells with uniform spherical nuclei that most likely represent a population of relatively radioresistant long-lived spermatogonia. As yet, these cells appear to be entirely quiescent with no cytological indication of any impending regenerative effort. The tubule lumens contain varying amounts of cellular debris, representing cast-off, degenerating elements of all phases of spermatogenesis. There is nothing to suggest any persistence of active spermatogenic maturation. There is some condensation and compaction of both the basement membrane and the laminated concentric connective-tissue cells that surround the basement membrane. This gives the impression of actual hypertrophy of the tubule sheath. The interstitial cells are perhaps somewhat smaller than usual; however, most appear to be within the normal limits insofar as size and morphology are concerned. The nutrient arterioles show varying degrees of thickening of the vascular walls, principally due to a fibrillar fenestration of the smooth-muscle laminations along with some vacuolation in the media and in the subintimal areas.

HEART. No relevant changes are present in the muscle fibers or the nutrient vessels coursing through the interstitial tissues which might be considered as either direct or indirect effects of ionizing radiation. There is a reactive hyperplasia of the epicardium with proliferation of the mesenchymal cells, the deposition of a dense fibrin material, and the elaboration of a zone of subepicardial fibrous tissue. There is a slight to moderate infiltrate of mononuclear cells. The epicardial adipose tissue and the vessels lying between the epicardium and the myocardium display no features that might be related to radiation response, and it is probable that the observed epicardial changes are the result of an unrelated condition.

LUNG. A normal lacelike architecture is preserved. There is some dilation of the alveolar spaces, which, however, contain no fluid or cell infiltrate. The vessels and the air ducts are unremarkable.

KIDNEYS. The architecture of the renal parenchyma is undisturbed. The nephrons are of normal configuration. There is cloudy swelling of the tubular epithelium, but this is of a degree that is considered not unusual in necropsies in an individual having a stormy terminal course. There is no interstitial edema or hemorrhage. Some of the afferent arterioles show localized minimal thickening of the walls due primarily to small focal deposits of hyalin material in the intimal zone. Some sections show large, wedge-shaped areas of parenchymal infarction involving both cortex and medulla with tissue survival in a narrow subcapsular zone. Occasional fibrin thrombi are noted in the associated vessels.

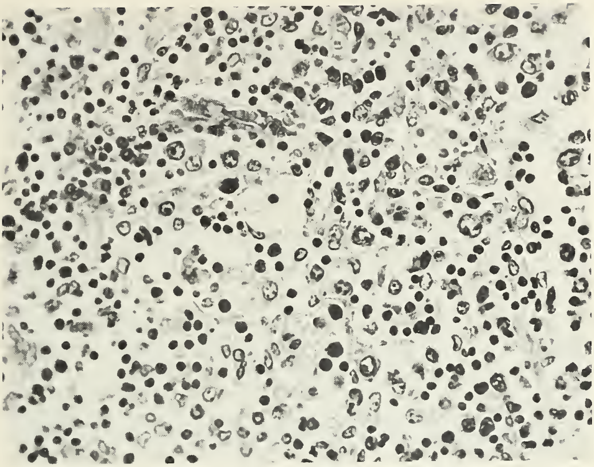


Fig. 1.53 Lymph node. Cell atypia in regenerating lymphoid parenchyma.

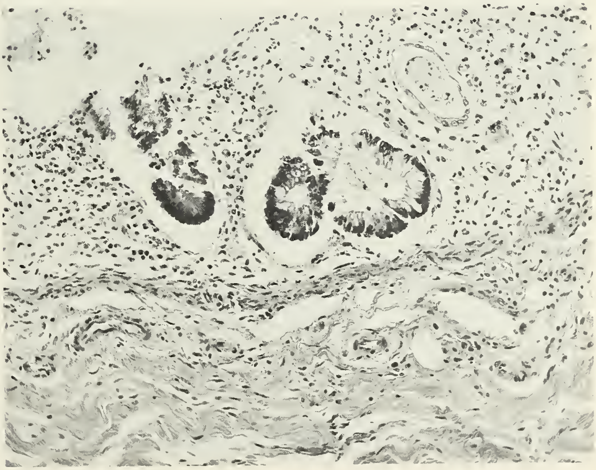


Fig. 1.54 Intestine. Regenerating epithelium in depleted mucosa.

Fig. 1.55 Testis. Tubule atrophy.

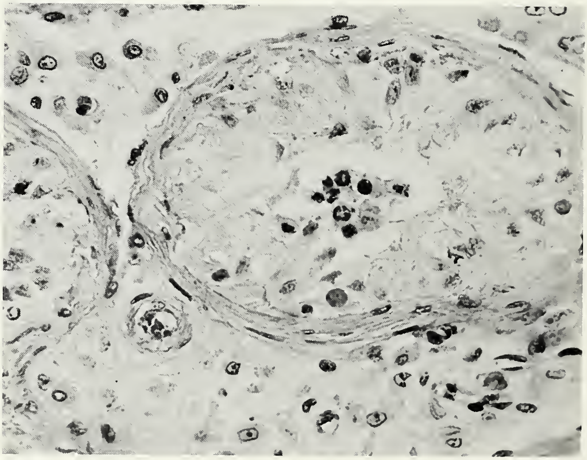


Fig. 1.56 Testis. Deletion of spermatogenesis.

URINARY BLADDER. There is some edema of the muscle layers; however, the submucosa is compact and without inflammatory infiltrate, edema, or hemorrhage. The majority of the transitional epithelium has sloughed, probably terminally or postmortem. Small foci of residual epithelium are normal in every respect.

SKIN. There are large areas of total destruction of the epidermis. The bases of the denuded areas consist of degenerative cellular debris along with condensation, hyalinization, and irregular discontinuity of the underlying collagen and elastic fibers. Little or no inflammatory infiltrate is present although aggregates of bacteria are seen in the debris. Interspersed between the areas of denudation are islands of epidermis which vary in depth and exhibit moderate hyperkeratosis and parakeratosis (Fig. 1.57). For the most part, the basal-cell layer is well populated, although many of these cells are pleomorphic. Mitotic figures are relatively common, some appearing abnormal. Moderate cell pleomorphism exists throughout the remainder of the epidermis. In contrast to this regenerative effort of the surface epithelium, the lining sheath cells of the hair follicles show only sporadic attempts at regeneration, and the majority of the cells are markedly atypical with degenerative nuclear and cytoplasmic changes and abnormal cell keratinization (Fig. 1.58). Much of this cell debris has plugged the hair-shaft canal and resulted in a dilation of this structure. Similar but less pronounced effects are observed in the ducts of the sweat and sebaceous glands, although the glands themselves continue to reveal only a slowly progressive response with an increased proportion of degenerating lining epithelial cells exhibiting cytoplasmic vacuolation. In the outer dermis there is a moderate ectasia of the superficial vessels; a minimal infiltration by monocytic cells, particularly plasma cells; and some blunting and fragmentation of the underlying collagen.

Case E (980029)

Satisfactory material from this case was very limited.

SPLEEN. The red pulp predominates although the regenerating white pulp areas seem to be expanding from their perivascular location (Fig. 1.59). The majority of the cells in the white pulp are of the lymphocytic series, principally small and medium-sized although a few large lymphocytes and apparent primitive forms are noted. Occasional attempts at mitotic activity are observed (Fig. 1.60). There are also large mononuclear cells with folded or indented nuclei and a scattering of granulocytes not only in the white pulp but throughout the splenic parenchyma. A significant number of the mononuclear cells, particularly in the white pulp, are of atypical configuration, probably reflecting mitotically connected radiation injury. The sheathed arteries are thick walled as a result of swelling of smooth-muscle cells plus an increase in the width of the intima and some deposition in the subintimal region of a dense hyaline substance. This vascular alteration is not as obvious as in the other cases, reflecting perhaps a reversion toward normal with the passage of time. It suggests the possibility that much, if not all, of this vascular change is either of a reversible nature or is dependent on dose absorbed.

INTESTINE. The appearance of the small intestine in this particular case is in sharp contrast to that of case D, although the time differential is relatively slight. The

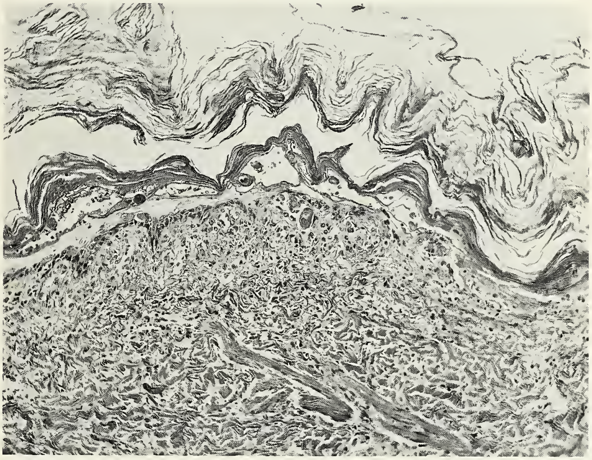


Fig. 1.57 Skin. Marked epidermal destruction with focal regenerative efforts.

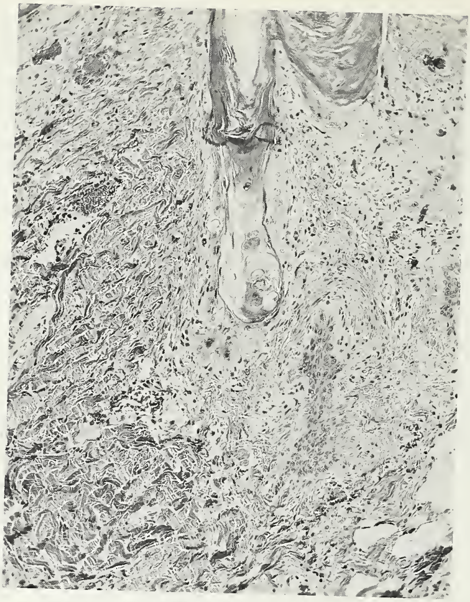


Fig. 1.58 Skin. Loss of hair shaft and epidermal atypism.

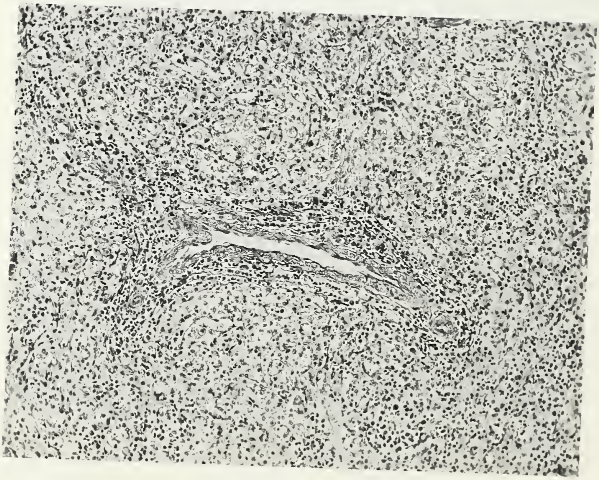


Fig. 1.59 Spleen. Early perivascular mononuclear regeneration.

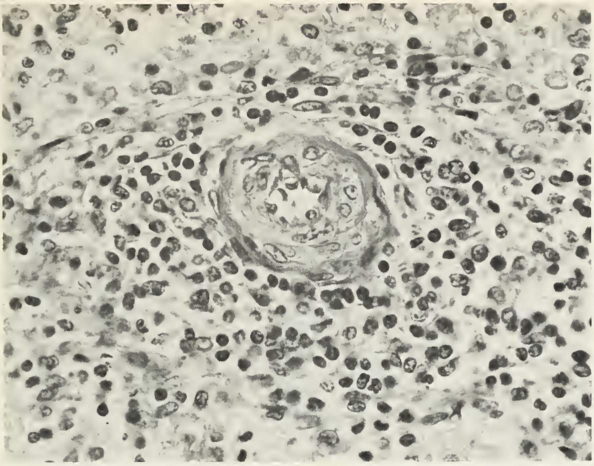


Fig. 1.60 Spleen. Many of these newly formed cells are abnormal.

architecture here is little if at all disturbed with perhaps a vague irregularity to the usually uniform pattern of villi and crypts. The lining epithelium appears to have a normal complement of principal cells, and these cells are remarkable for their uniformity of size and configuration. The small Paneth's cell population is similarly unremarkable. Mitotic figures in the proliferative zone of the crypts are of usual frequency; both lamina propria and submucosa contain a moderate infiltrate of lymphocytes, plasma cells, and a few polymorphonuclear leukocytes. In brief, there is nothing here of a histologic nature which might suggest an excessive exposure to ionizing radiation.

TESTIS. The atrophy of the spermatogenic epithelium is essentially total. The seminiferous tubules are reduced by about one-half in overall diameter with a relative thickening of the basement membrane and enclosing connective-tissue sheath (Fig. 1.61). The inner lining of the seminiferous tubules consists of a single layer of Sertoli cells, oriented radially with their uniformly ovoid nuclei situated in a parabasal position (Fig. 1.62). The cytoplasm is somewhat vesicular and fibrillary in structure with the luminal borders poorly defined. In close apposition to the basement membrane and situated between the bases of Sertoli cells are occasional rounded cells that resemble intermitotic spermatogonia. Some of the tubule lumens are partially occluded by an amorphous anuclear substance. The interstitial tissues are loose and edematous, with the cells of Leydig unremarkable except for a reduction in their average size. The small interstitial arterioles disclose enlarged endothelial cells and swollen and vacuolated smooth-muscle cells.

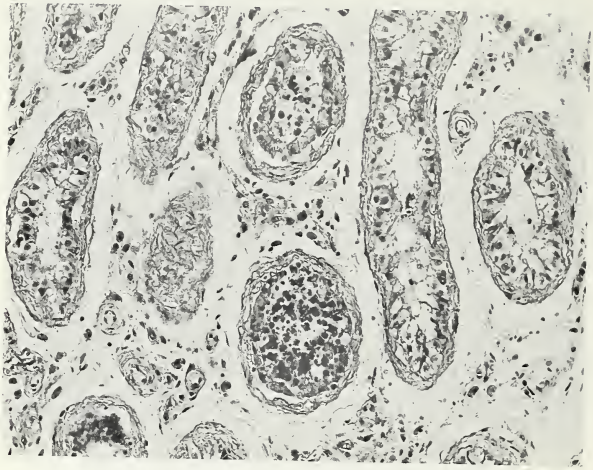


Fig. 1.61 Testis. Marked tubule atrophy.

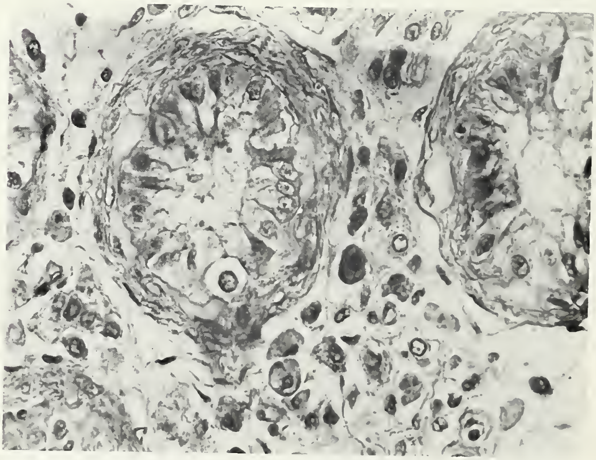


Fig. 1.62 Testis. Seminiferous tubules lined by Sertoli cells.

ADDENDUM: EARLY EFFECTS ON THE SPLEEN IN EXPERIMENTAL PRIMATES

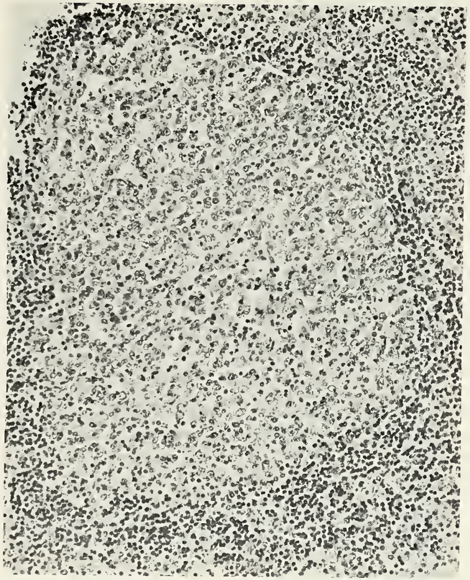


Fig. 1.63 Dose, 8000 rads; time after exposure, $3\frac{1}{2}$ hr. The small lymphocytes within the germinal center and in the heavily populated zone about the center exhibit moderate to severe pyknosis. Phagocytosis of damaged cells has just begun.

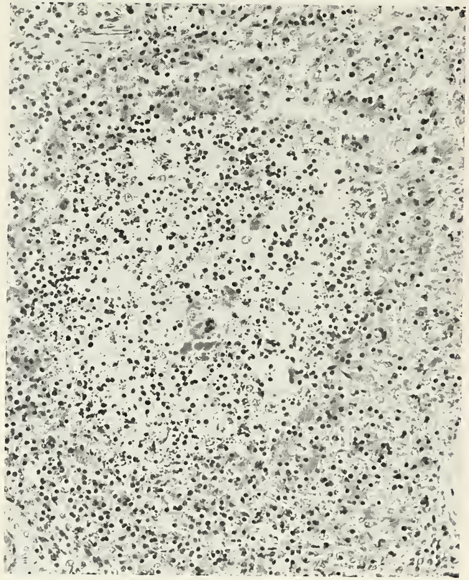


Fig. 1.64 Dose, 11,000 rads; time after exposure, $15\frac{1}{2}$ hr. The maximum lymphocyte destruction has passed, and macrophages are sweeping the white pulp clear of cell debris.

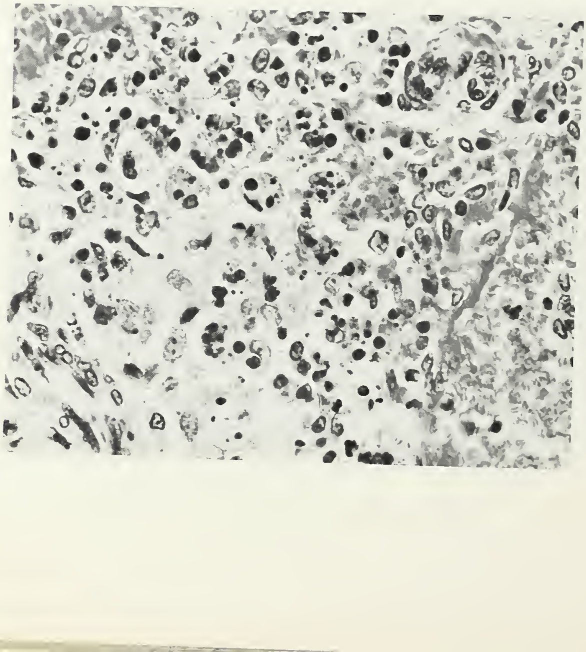


Fig. 1.65 Dose, 8000 rads; time after exposure, 18 hr. Macrophages are abundant and active. These scavenger cells are distended with engulfed pyknotic cells, cell fragments, and vacuoles.

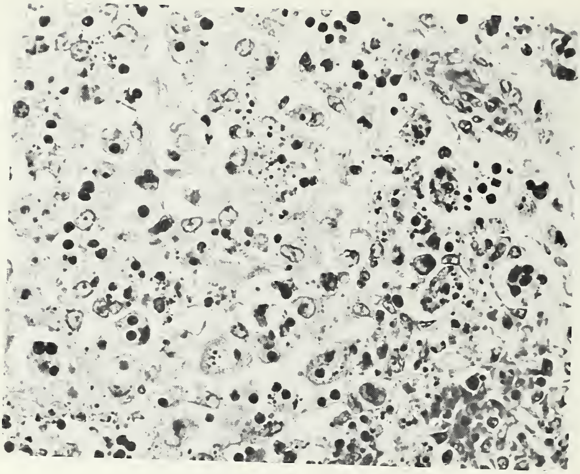


Fig. 1.66 See caption for Fig. 1.65.

Fig. 1.67 Dose, 8000 rads; time after exposure, 19 hr. Widespread cell degeneration continues with a heavier concentration of damaged cells and cell debris near the periphery of the germinal center.

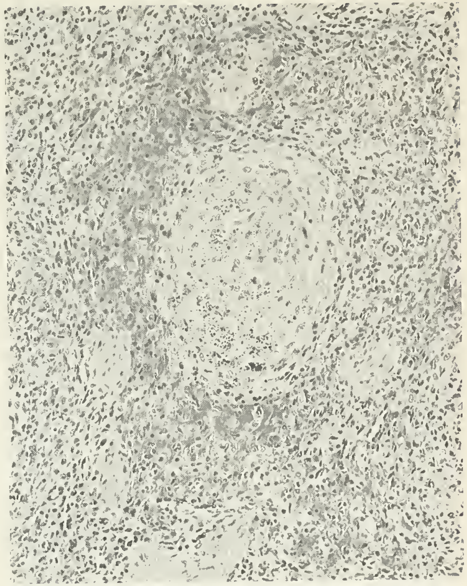


Fig. 1.68 Dose, 5000 rads; time after exposure, 21 hr. Most of the debris is now within macrophages with only scattered cell fragments lying free in the depopulated stroma. There is congestion of the sinusoids adjacent to the center.

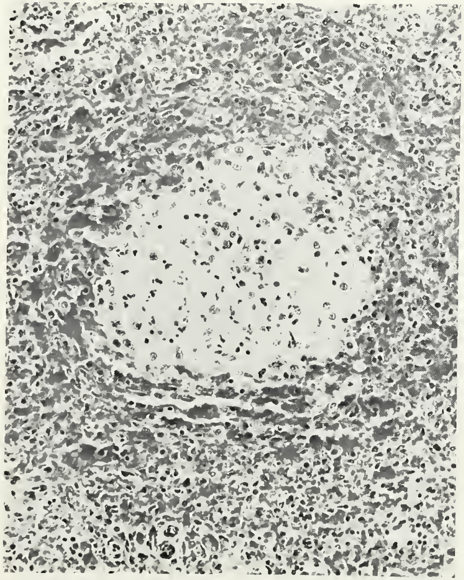


Fig. 1.69 Dose, 11,000 rads; time after exposure, 26 hr. The nodule has been swept clear. The reticular cells and histiocytes are reverting to a more normal resting morphologic state. There is a cuff of congested sinusoids.

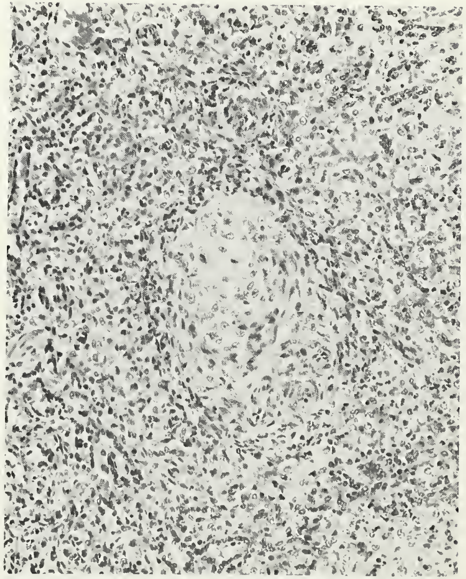


Fig. 1.70 Dose, 5250 rads; time after exposure, 50 hr. The spleen is now in its condition of lymphocyte depletion. The white pulp is poorly defined and consists primarily of a compact nidus of concentrically oriented reticular cells about an associated arteriole.

Chapter 2
Skin

NORMAL STRUCTURE AND FUNCTION

The skin is a tough yet resilient covering that forms a competent protective barrier against a broad spectrum of injurious agents and influences. It is in continuity with the mucous membranes lining the several openings that enter the body.

The skin, in addition to affording effective protection, also aids in the regulation of body temperature, excretes the products of its sweat and sebaceous glands, and reacts to various sensory stimuli.

The two major anatomical divisions of the skin are the relatively thin *epidermis* and the underlying *dermis.*

Epidermis

The epidermis is a stratified squamous epithelium. This is a relatively rapid cell-renewal system that consists of the following layers:

Germinal layer: Proliferative basal cells surmounted by differentiating or maturing cells.

Granular layer: More pronounced polarization of cells in parallel with skin surface with appearance of intracellular droplets of keratin.

Clear layer: Flattened, dead cells with more advanced keratinization. Nuclear definition disappearing.

Horny layer: Compact cornified structures with little or no cell detail.

Dermis

The dermis is separated from the epidermis by basement membrane. This dense connective-tissue foundation contains the following elements:

1. Interwoven bundles of collagen and elastic fibers.
2. Vascular network (blood and lymphatic) as well as fine radicles of nerves, many terminating in sense organs.
3. Hair follicles and sebaceous glands.
4. Sweat glands.
5. The deep dermal zone invests islands of fat cells and merges indistinctly with the subcutaneous fat and the fascial planes.

CLINICAL SYNDROME

Acute Effects (During Radiotherapy and Immediately Posttherapy)

1st week: Asymptomatic.
Faint erythema (often difficult to identify).

2nd week: Asymptomatic.
Development of true erythema.
Progressive epilation.
Suppression of sweating.
Diminished sebaceous gland secretion.

3rd week: Skin red, warm, and edematous.
Painful to touch.
Burning sensation.
Above usually sharply limited to radiation field.

4th week: Moist desquamation develops with discomfort at a maximum (oozing surface).
If the course of radiation has been halted (at about the 3000-rad level), the result may be a *dry* desquamation with some increased pigmentation (less painful and more pruritic).

5th week: With completion of the radiation therapy, reepithelization proceeds slowly (epidermal "islands" and from margins).

Early Delayed Effects (From Several Weeks to Several Months Posttherapy)

1. Very slowly progressing atrophy.
2. Loss of pigment with subsequent vitiligo (especially noticeable in dark-complected individuals).
3. Ulcerations possible with repeated trauma, on surfaces over bone protuberances, or where there is excessive friction.

Comment: Differentiation of these ulcers from recurrent cancer may require a biopsy of the ulcer edge. If conservative therapy fails, a skin graft may become necessary.

Late Delayed Effects (1 to 6 Years or More)

1. Atrophy and loss of elasticity (restricted to field of radiation).

2. Telangiectasia (spidery pattern readily visible beneath thin epidermis).

3. Suppressed glandular function (dry and often scaling surface).

4. Epilation.

5. Brittle nails.

6. Ulceration (persistent and painful and usually difficult to control and heal).

7. Scarring (sometimes with deformities and limitation of motion produced by contraction) results from plaque-like area of deep dense fibrosis. Subsequent surgery in such an area is difficult and marked by poor primary healing.

8. Development of malignant change.

Very Late Effects (Beyond Several Years)

It is perhaps only academic to attempt a separation of this group of delayed sequelae from the above chronic radiation dermatopathy. One would be more justified in ascribing these late effects to indirect or secondary responses.

Various keratoses are often associated with ulceration. Most of these lesions can be justifiably termed precancerous. These cases usually fall into two categories of "preconditioning."

1. *Occupational* (late radiation dermatopathies): Dentists, physicians, radiation technicians, nuclear scientists, etc.

2. *Therapeutic* (late radiation dermatopathies): Most individuals treated for benign conditions (dermatitis, lymphadenopathy, goiter, and benign tumors). This is actually a false interpretation since it is probable that many patients irradiated for malignancy might also develop late dermatopathies if they are fortunate enough to survive the original tumor.

3. *Accidental* (late radiation dermatopathies): This is not yet an adequately proven group for human exposure; however, individuals involved in direct nuclear reaction or in radioactive fallout may also develop lesions of a cancerous or precancerous nature.

Comment: Differential diagnosis of radiation-induced cancer and recurrent cancer should not prove too difficult. Radiation-induced cancer is generally in the midst of severe long-standing radiation change. Recurrent cancer would generally develop relatively early and occur primarily at the edge of the scarred, atrophic area where the dose was rapidly attenuated.

RADIATION HISTOPATHOLOGY (DERMATOPATHY)

Because of its function as a highly effective barrier against a wide variety of agents (physical, chemical, and biological) that might be detrimental to the health of an individual, every possible effort is made to maintain the integrity of this first-line defense during and subsequent to a course of radiation therapy.

This problem had a relatively greater importance in the early days of radiotherapy when the lower energy levels and lack of proper filtration resulted in the absorption of large amounts of beam energy by the skin. More often than not this became the limiting factor in the amount of radiation that could be safely delivered at any given time to any given surface area—hence the now somewhat outdated term "erythema dose."

The advent of much more efficient and energetic sources of radiation, along with vastly improved beam filtration and methods of delivery, has resulted in a much smaller proportion of the ionizing energy being absorbed in the skin with a concomitant reduction in clinically significant irreversible injury.

Early Effects

The initial faint flush is probably a transient capillary dilation perhaps caused by the local response to individual cell destruction. Subsequent to this brief, acute response and leading up to the detection of the true erythema reaction, there is subclinical development of microvascular alterations of variable severity from reversible endothelial swelling and increased porosity to endothelial degeneration and thrombosis with occlusion.

True erythema is apparently related in part to arteriolar constriction and is associated with capillary dilation and edema with variable extravasation of leukocytes and erythrocytes.

Dry desquamation will usually develop just after the appearance of this true erythema and is contingent on the radiation exposure's being halted at this dose level (approximately 3000 rads).

It is mainly a reflection of the response of the germinative epidermal layer. Mitotic activity is greatly diminished, so cell replacement is reduced to near zero. The cells of the basal and parabasal layers become swollen and vacuolated. There is nuclear pleomorphism and binucleation. The epidermis becomes very thin with flattening of the papillae. The process of epidermal-cell maturation and keratinization is altered with the incomplete keratinization of the superficial cells producing desquamation in large macroscopic flakes rather than the small inconspicuous scale-like aggregates.

Under this condition of limited dose level, there is seldom any transepidermal break of continuity even though the depth of the epidermis may be reduced to but a few dyskeratotic cells.

Recovery of the epidermis will be nearly complete, although residual microvascular and connective-tissue changes may persist and even slowly progress over an extended period of time.

Moist desquamation may develop if the irradiation is continued to the level of about 4000 rads over a 4-week treatment period.

This severe form of acute radiation dermatitis is characterized by the formation of intercellular edema with accentuation of the intercellular bridges. Vesicles may form with these and often coalesce to produce bullae exterior to the basal-cell layer or actually beneath the basal cells, forcing the total epidermis away from the dermis. Some degree of inflammatory cell response may be evoked by this more pronounced cell degeneration.

The epidermis may slough, exposing the dermal surface, which becomes coated by a layer of fibrin.

At this dose level there will usually be a permanent epilation and greater destruction or atrophy of the glands.

With proper care and management, the denuded surface will become reepithelialized over the subsequent 1 to 2 weeks. The competence of this reparative process will depend on:

1. The severity of injury to the epidermal precursor or stem cells.
2. The adequacy of the microvasculature.
3. The structural support of the damaged dermal outer zone.
4. The avoidance of infection and trauma.

The epidermis is renewed by the proliferation of epithelium at the edges of the denuded area, from islands of surviving cells in the damaged zone, and from the epithelium of the hair follicles.

Frequently these early stages witness an increased elaboration of melanin by the melanocytes of the outer dermis. This pigment appears intracellularly and extracellularly in the epidermis.

If conditions are less than optimal for the repair mechanisms and particularly if the vasculature has been extensively compromised, an acute necrotic ulceration may develop. Occasionally, as a result of unintentional excessively high dose levels, there may be severe damage through the total skin thickness which sometimes involves deep adipose tissue, fascial planes, and muscles. Repair of this massive tissue destruction will be by secondary intent with disfiguring and debilitating scarring progressing inward and outward from the edges and base.

Delayed Effects

Generally there is a period of several months during which little is observed clinically. The epidermis has been reconstituted to some degree and to outward appearances has stabilized.

The overt latency of this period belies the rather marked changes that may be taking place at all levels of the skin.

Of particular importance is the functional efficiency of the vascular system. Early in this period there is noted reestablishment of vascular channels and neovascularization as a part of the recovery of the acute radiation dermatopathy. As time passes, however, sclerotic changes become more evident in the small arteries and arterioles, and the resultant relative ischemia in the dependent tissues causes progressive densification of the connective tissues, reduction in competency of the microvasculature, and atrophy of related structures, including the epidermis and adnexal glands.

REFERENCES

Allen, A. C., 1954, *The Skin*, The C. V. Mosby Company, St. Louis, Mo.

Chu, F. C. H., 1966, Radiation Therapy of Breast Cancer, *Clin. Obstet. Gynecol.*, **9**: 221-234.

Cramer, L. M., J. H. Waite, J. H. Edgcomb, C. C. Powell, J. H. Tuohy, E. J. VanScott, and R. R. Smith, 1959, Burn Following Accidental Exposure to High Energy Radiation, *Ann. Surg.*, **149**: 286-293.

Devik, F., 1955, A Study of the Local Roentgen Reaction on the Skin of Mice, with Special Reference to the Vascular Effects, *Acta Radiol., Suppl.*, **119**: 1-72.

Edmondson, P. W., 1968, Severe Fibrosis of the Skin and Sub-Dermal Tissue of Goats After Single Exposures to Fast Neutrons, *Int. J. Radiat. Biol.*, **14**: 263-270.

Hartwell, S. W., Jr., W. Huger, Jr., and K. Pickrell, 1964, Radiation Dermatitis and Radiogenic Neoplasms of the Hands, *Ann. Surg.*, **160**: 828-834.

Hempelmann, L. H., H. Lisco, and J. Hoffman, 1952, The Acute Radiation Syndrome: A Study of Nine Cases and a Review of the Problem, *Ann. Intern. Med.*, **36**: 279-510.

Hurley, J. V., K. N. Ham, and G. B. Ryan, 1969, The Mechanism of the Delayed Response to X-Irradiation of the Skin of Hairless Mice and of Rats, *Pathology*, **1**: 3-18.

Knowlton, N. P., Jr., et al., 1949, Beta Ray Burns of Human Skin, *J. Amer. Med. Ass.*, **141**: 239.

Liegner, L. M., and N. J. Michaud, 1961, Skin and Subcutaneous Reactions Induced by Supervoltage Irradiation, *Amer. J. Roentgenol., Radium Ther. Nucl. Med.*, **85**: 533-549.

Lowell, D. M., R. G. Martineau, and S. B. Luria, 1968, Carcinoma of the Male Breast Following Radiation, *Cancer*, **22**: 581-586.

Martin, H., E. Strong, and R. H. Spiro, 1970, Radiation-Induced Skin Cancer of the Head and Neck, *Cancer*, **25**: 61-71.

Maxfield, W. S., and W. P. Coleman, 1969, Cutaneous Reactions After Radiation Therapy: Report of 7 Cases, *Amer. J. Roentgenol., Radium Ther. Nucl. Med.*, **105**: 636-643.

Neuman, Z., N. Ben-Hur, and J. Shulman, 1963, The Relationship Between Radiation Injury to the Skin and Subsequent Malignant Change, *Surg. Gynecol. Obstet.*, **117**: 559-562.

Pack, G. T., and J. Davis, 1965, Radiation Cancer of the Skin, *Radiology*, **84**: 436-441.

Pettit, V. D., J. T. Chamness, and L. V. Ackerman, 1954, Fibromatosis and Fibrosarcoma Following Irradiation Therapy, *Cancer*, **7**: 149-157.

Rachmaninoff, N., J. R. McDonald, and J. D. Cook, 1961, Sarcoma-Like Tumors of the Skin Following Irradiation, *Amer. J. Clin. Pathol.*, **36**: 427-437.

Samitz, M. H., 1967, Pseudosarcoma. Pseudomalignant Neoplasm as a Consequence of Radiodermatitis, *Arch. Dermatol.*, **96**: 283-285.

Tapley, N. duV., and G. H. Feelcher, 1965, Skin Reactions and Tissue Heterogeneity in Electron Beam Therapy. I. Clinical Experience, *Radiology*, **84**: 812-816.

Teloh, H. A., M. L. Mason, and M. C. Wheelock, 1950, A Histopathologic Study of Radiation Injuries of the Skin, *Surg. Gynecol. Obstet.*, **90**: 335-348.

Tessmer, C. F., H. L. Andrews, and F. L. Jennings, 1961, Unique Tissue Depth Response to Electron Irradiation, *Radiat. Res.*, **14**: 167-173.

Totten, R. S., et al., 1957, Pre-Existing Roentgen-Ray Dermatitis in Patients with Skin Cancer, *Cancer*, **10**: 1024-1030.

Warren, S., 1943, Effects of Radiation on Normal Tissues. XII. Effects on Skin, *Arch. Pathol.*, **35**: 340-347.

Wells, F. R., 1963, The Lymphatic Vessels in Radiodermatitis: A Clinical and Experimental Study, *Brit. J. Plast. Surg.*, **16**: 243-256.

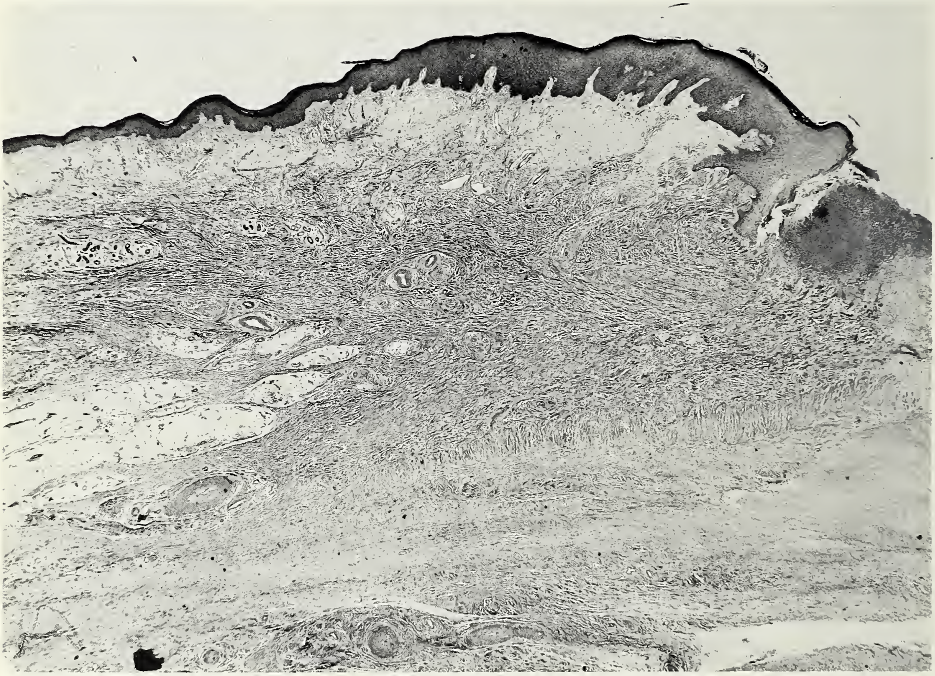
Fig. 2.1 Acute radiation dermatitis. (a) This diagram represents normal epidermis and outer dermis. The basal, or germinal, layer consists of relatively uniform cells oriented perpendicularly to the epidermo–dermal junction. Cell division for the epidermal-renewal process occurs here and in the parabasal cells, which are subjacent to the granular layer. The cells of the granular layer are flattened and polarized parallel with the skin surface and begin to display a few droplets of keratohyalin. The cells of these two lower layers are distinctly separated but with many fine intercellular bridges. Small stellate or polyhedral melanocytes can be found in the outer dermis and lower epidermis. Surmounting the granular cells is the clear layer which consists of flattened, dead cells with greater numbers of keratin granules and diminishing nuclear definition. The outer horny layer varies in depth from area to area on the body surface. It is made up of cornified compressed plates having no cell detail which are continually being sloughed from the surface.

(b) This diagram illustrates the acute response to irradiation. The cells of the basal layer are decreased in number and have lost most of their cohesion as well as their intercellular bridging. Both intracellular and extracellular vacuolation are usually present. These vacuoles may coalesce to form vesicles that lift these damaged basal cells from the underlying dermis. There is an arrest of mitoses in this proliferative zone with the effect that no new cells are available to replace those lost through continued maturation and attrition, and the epidermal-cell depth diminishes. The irradiation produces some degree of direct cell damage in the postmitotic maturing cells; however, the most severe cytopathology is related to radiation changes in cells entering or in mitosis at the time of exposure. If there is not prompt destruction of the dividing cells, the daughters of such affected mitoses may be distinctly abnormal and often have greatly shortened life-spans. Melanocytes may be at first increased in number both in the epidermis and in the outer dermis. The dermal collagen and elastic fibers are initially thickened.


HORNY LAYER
CLEAR LAYER
GRANULAR LAYER
MALPIGHIAN LAYER
PARABASAL CELLS
BASAL CELLS

Fig. 2.2 Early delayed radiation dermatopathy. **(a)** Occasionally the circumstances of the irradiation result in a greater degree of early injury than had been anticipated. This photomicrograph depicts the edge of a large ulcerative defect in a case where an excessive dose of irradiation was inadvertently administered. The edge is not cratered as is generally true of the late delayed lesions. There is coagulative necrosis at the ulcer surface, and the underlying connective tissue is swollen, dense, and hypocellular. Beneath the edge is vascular congestion and some focal hemorrhage. Note the reactive epidermal hyperplasia in the basal and parabasal layers.

(b) Away from the area of greatest injury there is still extensive degenerative change in the dermis. The recuperative capacity of the epidermis, however, has resulted in perpetuation of this protective barrier. Adnexal structures are not present in these sites of severe damage.

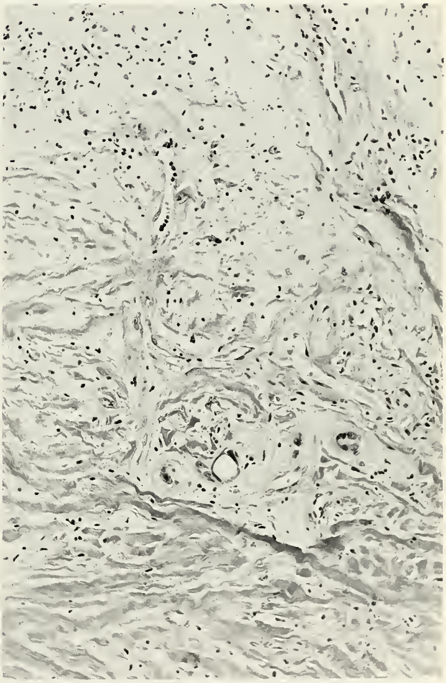


(a)

Fig. 2.3 Late delayed radiation dermatopathy. (a) This is a low-power photomicrograph through one edge of a chronic radiation ulcer. The ulcer is cratered and has a base of necrotic debris and fibrin resting on a large and deep focus of fibrosis and hyaline degeneration. The epidermis at the rim of the ulcer is hyperplastic, and this overgrowth extends outward from the ulcer for several millimeters. The outer dermis displays some exaggerated coagulation degeneration of collagen, and the midzone and deep dermis reveal severe fibrosis disrupting normal integumental architecture. Both superficial and deep vessels are markedly sclerotic. No sweat glands are identified in the dense fibrosis adjacent to the ulcer. Further distant, however, these sweat glands make their appearance. Close in they are severely atrophic but assume a more normal structure several millimeters out from the ulcer.

(b)

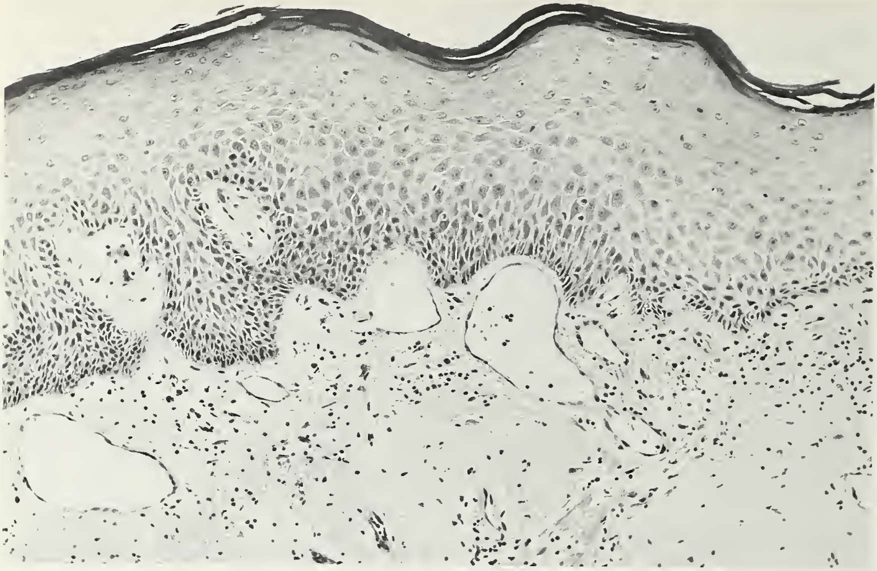
(b) This high-power view of the ulcer edge accentuates the abrupt interruption of the epidermis and the marked epithelial hyperplasia. The epidermal rete pegs are irregular. The fibrin coagulum within the ulcer concavity contains many leukocytes and an abundance of cell debris.



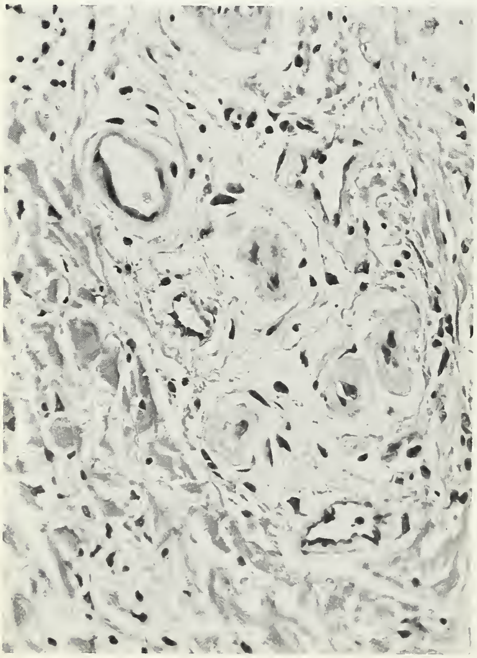
(c)

(c) A short distance from the ulcer base, the severity of the dermal response to the radiation is manifest in the degeneration of the connective-tissue matrix and the intervention of dense fibrous tissue. In the center of this photomicrograph is the residuum of a sweat gland.

(Figure continues on following page.)



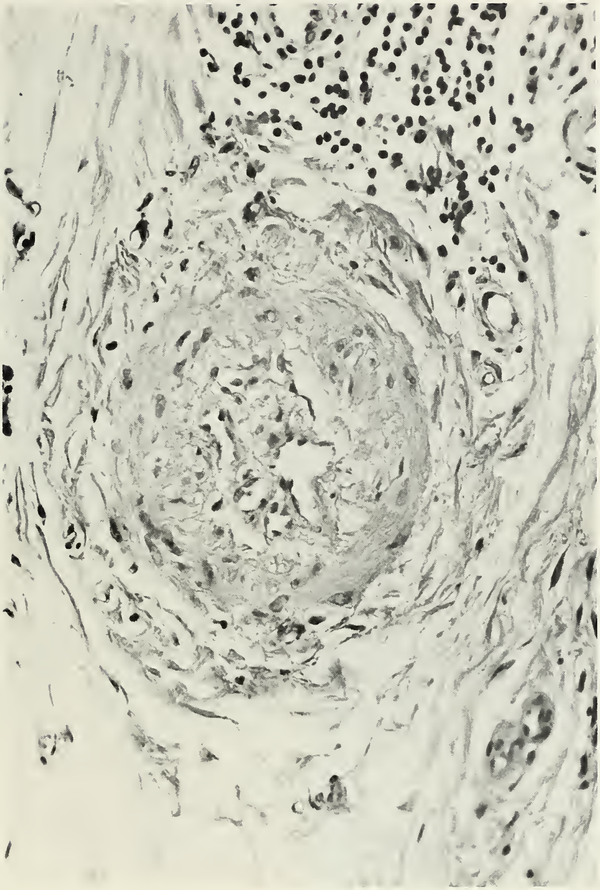
(d)



(d) Away from the ulcer the increased depth of the epidermis and the irregular rete are still in evidence. The papillary zone of the dermis contains telangiectatic vessels and a slight lymphocytic- and plasma-cell infiltrate. Occasional large, bizarre fibroblasts are seen.

(e) Although the radiation ulcer is the lesion of greatest concern, it is important to assess the extent of radiation damage at the line of excision. This photomicrograph shows that even sweat glands relatively distant from the ulcer exhibit severe morphologic alterations. The lining epithelial cells have been destroyed, and the somewhat more resistant "myoepithelial" cells are greatly reduced in number and are pleomorphic. These few residual cells rest on a very thick basement membrane.

(e)

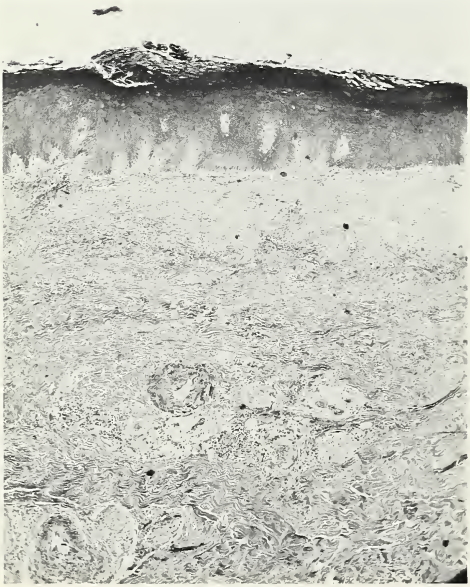


(f)

(f) This photomicrograph shows a deep medium-size artery with greatly thickened walls which has undergone occlusion and subsequent recanalization. There is an adjacent infiltrate consisting almost entirely of lymphocytes.

(a)

Fig. 2.4 Late delayed radiation dermatopathy. (a) This low-power photomicrograph shows a large ulcer with thick, dense surface exudate and an underlying necrotic and hemorrhagic base. The fibrosis extends deep, involving all layers of the dermis and the underlying adipose tissues. The vascular sclerosis of the large deep arteries as well as that of the smaller vessels is obvious. Adnexal structures are not apparent. The epidermis at the ulcer edge is hyperplastic with large, irregular rete dipping into the dermis. This thickened epithelium extends the length of the section.



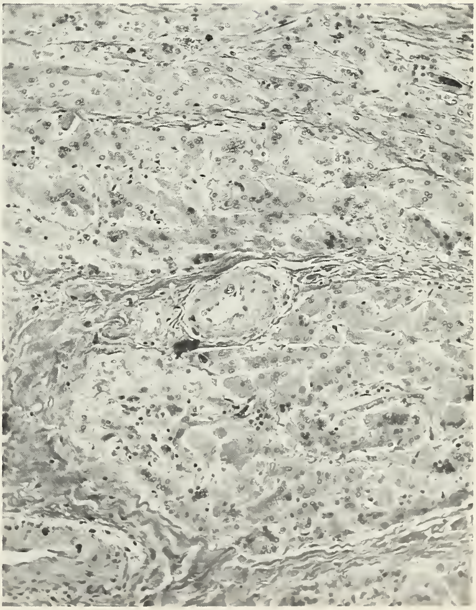
(b) Away from the ulcerated area of severest injury, scattered poorly delineated sweat glands can be identified. These structures lie deep in the middermis zone surrounded and almost obscured by the dense connective-tissue matrix and the increasing scarring.

(b)

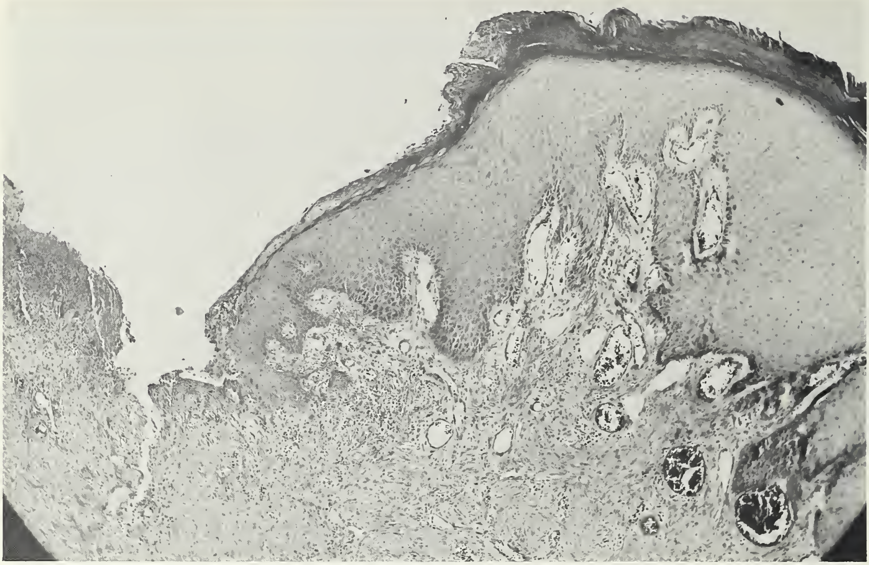
(c)

(c) A high-power photomicrograph of this gland area shows very atrophic residual glands in an edematous stroma. There is a moderate infiltration of lymphocytes in the contiguous loose connective tissue trabeculae. Near the center is a prominent small artery that is markedly sclerotic.

(d) It is not uncommon to find that the radiation damage has penetrated beyond the deep dermis and underlying adipose layer and involves even more remote structures, such as fascia and superficial striated muscle. This photomicrograph illustrates changes in muscle with variable fiber atrophy alternating with swollen muscle cells, some having clustered nuclei. The injured cytoplasm may remain fibrillary or assume a ground-glass or hyaline appearance. Fibrous trabeculations are broadened and are more conspicuous. Associated vessels are moderately sclerosed.

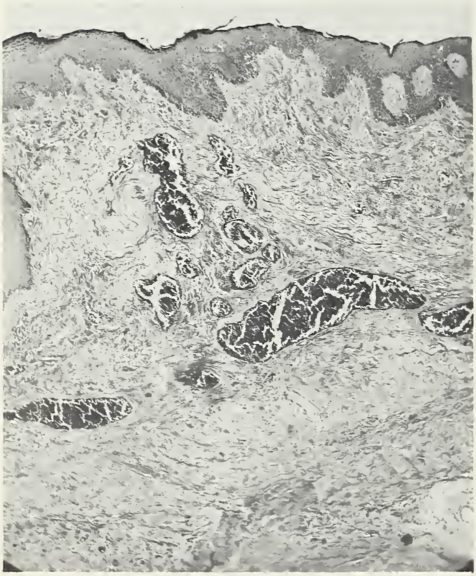


(d)



(a)

Fig. 2.5 Late delayed radiation dermatopathy. (a) Telangiectasia of superficial vessels is a characteristic lesion in chronic radiation injury of most tissues. The loss of resiliency in adjacent stroma and the associated fibrosis, as well as damage to the vessel structure itself, may cause irregular dilation of the affected blood or lymphatic channel. This lesion generally involves only thin-wall vessels. The dermal papillae of this section of a radiation-induced ulcer display many telangiectatic vessels. It is unlikely that such a plexus of dilated vessels could be visible from the skin surface because of their relatively small size and the greatly thickened epidermis. It is probable, however, that they would impart a reddish coloration to the ulcer edge.



(b) Deeper vessels are also subject to this pathologic process and may attain such large size as to be readily discernible from the skin surface.

(b)

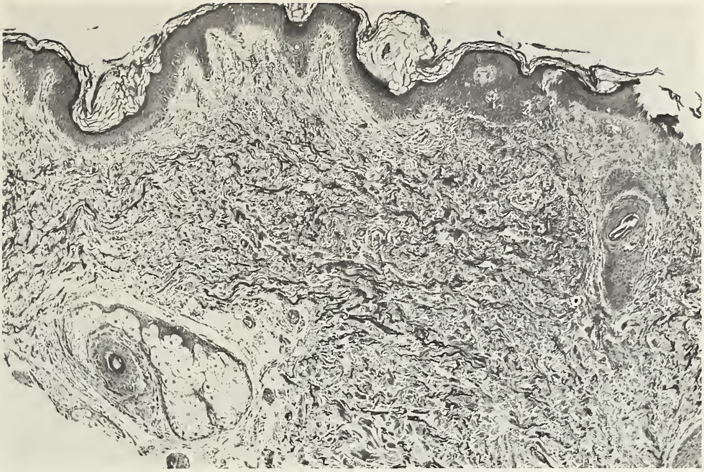
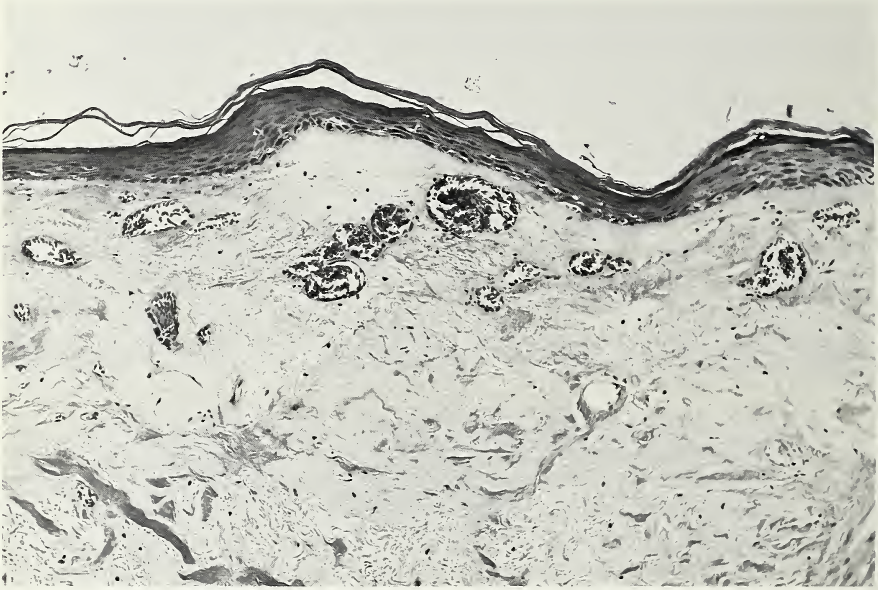


Fig. 2.6 Late delayed radiation dermatopathy. (a) This photomicrograph presents a section of skin several millimeters distant from the area of gross dermatopathy. In general, the histology is normal. The epidermal surface is somewhat rugate; however, the depth of the epidermis and its cell composition is unremarkable. The histochemical stain used here darkens the elastic fibers (Movat stain), which can be observed as a mesh of fine elongated strands intermingled with the collagen.

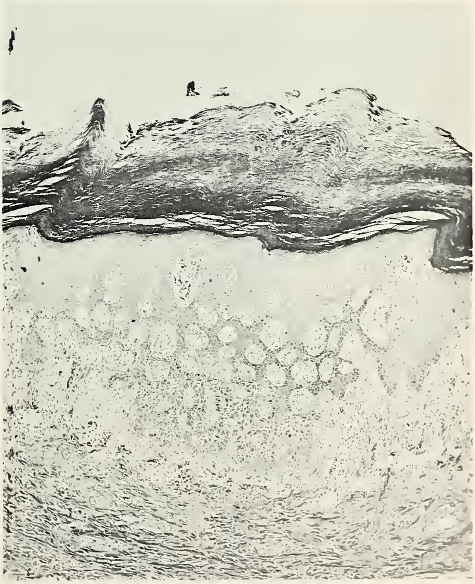
(b) This section is from the central area of severe chronic radiation dermatopathy. In contrast to the section shown in (a), there is dyskeratosis, hyperkeratosis, and moderate epidermal hyperplasia. The rete pegs are flattened, and some ectatic vessels are apparent. The collagen has become fused and hyalinized, and there is marked hypocellularity. There is obvious decrease in the elastic component of the dermis, with the fibers fractured, discontinuous, and variable in thickness. This histopathology is reflected clinically in the circumscribed area of blanched, scaling skin overlying a plaque-like, firm, nonresilient dermis. The correlative implication of increased susceptibility to trauma and refractive ulceration is readily apparent. Laceration or surgical incision through such an avascular, scarred area is to be avoided in view of the problem in primary repair.



2.7 Late delayed radiation dermatopathy. Late skin changes may assume either of two distinct histopathologic patterns or a variable blend of both types (atrophic and hypertrophic). The nature of the response probably depends largely on the degree of damage to the supporting dermis and the associated relative compromise of the microvasculature nourishing the overlying epidermis. Thus the intense skin injury generated by localized therapy given in a single series of exposures is more likely to become the atrophic form. This photomicrograph illustrates the thin, atrophic epidermis with a smooth but scaling outer surface and a loss of the rete peg pattern at the dermal interface. Telangiectasia is characteristic with the tortuous vascular pattern easily observed through the atrophic epidermis. The dermis is markedly hypocellular and consists of dense degenerative collagen and elastic tissues and fibrosis.

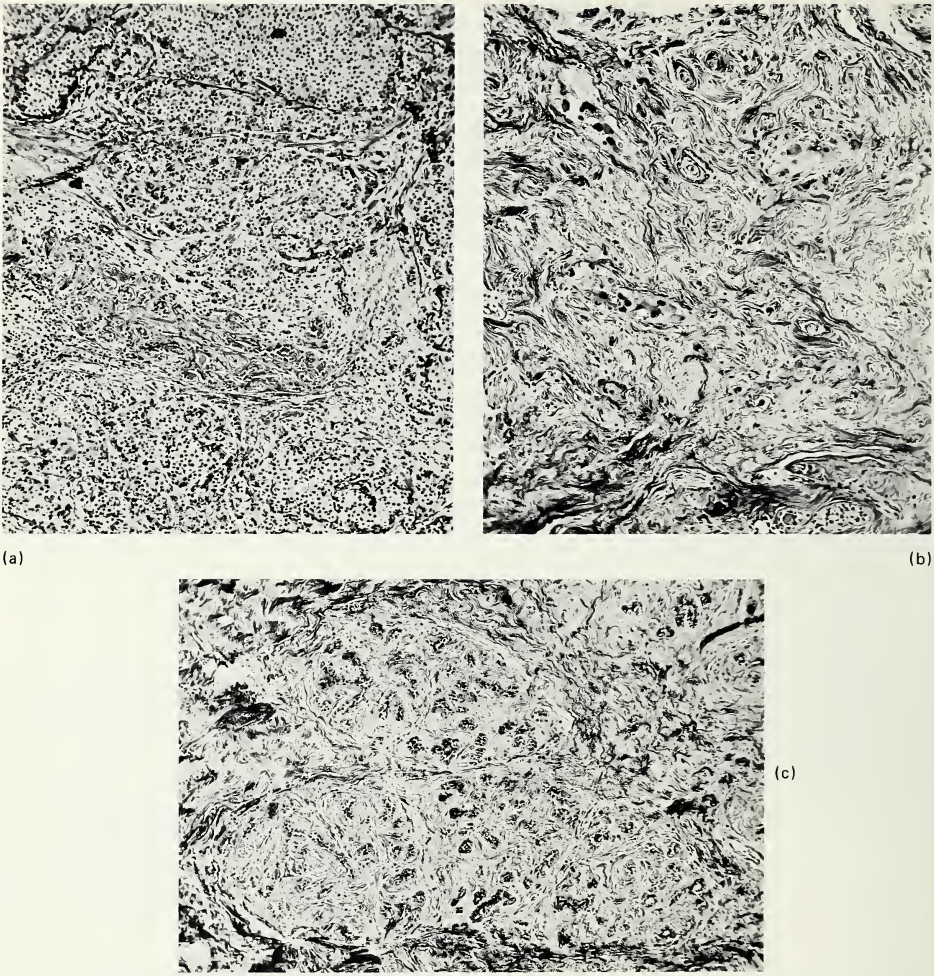
(a)

Fig. 2.8 Late delayed radiation dermatopathy (carcinogenesis). (a) At one time it was not uncommon to give repeated courses of relatively low dosage and energy for the treatment of benign diseases or conditions. This type of multiple exposures was also encountered in physicians, dentists, and radiation technicians who failed to take appropriate protective measures. Such a case is represented here. This is a low-power photomicrograph of one of many similar radiation keratoses that developed on this physician's hands. There is hyperplasia of the epidermis with hyperkeratosis, dyskeratosis, and irregular downward proliferation of the rete pegs. Fibrosis in the dermis is variable but generally increased beyond normal. The vessels are moderately sclerotic. At one point there is excessive and disorganized hyperplasia of the basal cells.



(b) At this point the basal hyperplasia has resulted in irregular interconnecting rete pegs and below this a disorganized overgrowth of cells that are more pleomorphic and with no polarity of composition. This focus of atypical proliferation represents a transition from radiation keratosis to squamous carcinoma. This transformation develops with sufficient frequency in late radiation dermatopathies of this type that they are generally considered precancerous and treated accordingly.

(b)



(a) (b) (c)

Fig. 2.9 Irradiation of mammary carcinoma. **(a)** The mammary gland, which is fundamentally a modified skin gland under hormonal control in the female, is a frequent site of carcinoma, and these lesions are often subjected to irradiation prior to surgery. This photomicrograph is a representative section of a biopsy from a large infiltrating duct carcinoma. The masses and cords of relatively uniform epithelial cells have pervaded the mammary parenchyma.

(b) This is a postirradiation photomicrograph of the same tumor. The infiltrating cords of tumor cells show marked degenerative changes (cytoplasmic vacuolation), marked pleomorphism, nuclear irregularity and dense hyperchromatism, and dissolution of cytoplasm and nuclear structure. The intervening stroma is densely fibrotic.

(c) Away from the tumor the mammary lobules also display radiation response. The gland epithelial cells are largely destroyed, and the underlying myoepithelial cells are distorted and degenerative. The basement membrane of the gland is very thick.

Chapter 3
Heart

NORMAL STRUCTURE AND FUNCTION

The heart is a rhythmically contracting, thick-walled, muscular pump responsible for the continuous circulation of blood through the diverse systems and organs of the body. It is a centrally situated component of the thoracic viscera, where it lies obliquely in the lower half of the mid-mediastinum. It is roughly conical in configuration with its apex canted toward the base of the left lung. The sternum and rib attachments protect it anteriorly, and the vertebrae and ribs make up the posterior bony bulwark. Laterally the heart is partially enveloped by the lungs. The whole of this vital organ, including the bases of the great vessels, is enclosed within a tough protective pliable sac. The pericardial cavity thus formed is a potential space. Under normal circumstances the serous membrane of the pericardium is in contact with the serous layer of the epicardium. Friction between the surfaces is minimized by the slight amount of serous fluid that is normally present.

This remarkably efficient pumping station consists of four main chambers with the thick-walled ventricles providing the primary driving force for propelling blood through the capillary network of the respiratory parenchyma (pulmonary circulation) and the abundant vascularity of the other body tissues (systemic circulation). The base of the heart faces cephalad somewhat posteriorly and to the right. It consists of the less muscular auricular reservoirs and the major afferent and efferent vascular trunks.

The heart, because of its relatively high metabolic demands, is richly vascularized with the blood supplied via the major coronary vessels that arise in the aortic sinuses. The return venous circulation collects in the coronary sinus, which empties into the right auricle.

Special mention should be made of the lymphatic circulation of the heart because of the significant frequency of its involvement by retrograde tumor embolization and the possible relation of this occurrence to the development of pericardial effusion.

There are three components to the lymphatic system of the heart: subepicardial, myocardial, and subendocardial. The subepicardial lymphatics lie in a single plane in the connective tissue between the myocardium and the epicardium. The myocardial lymphatics are of relatively uniform caliber and are diffusely distributed in a three-dimensional roughly rectangular or rhomboid pattern throughout the entire myocardium. Short lymphatic vessels connect directly to the subepicardial lymphatic capillaries that overlie the interfascicular depressions. The subendocardial lymphatics form a single-plane plexus which lies parallel to the endocardial surface and which communicates via short branches with the deepest vessels of the myocardial system.

The lymphatic drainage of the entire cardiac wall is therefore directed toward the major collecting trunks that lie in the anterior and posterior longitudinal sulci. These tributaries join in the vicinity of the coronary sulcus and pass cephalad behind the pulmonary artery to drain into the tracheobronchial lymph nodes.

HISTOLOGY

The wall of the heart is markedly variable in depth from the very thin auricles to the thick muscular left ventricle. It consists of three clearly defined layers: endocardium, myocardium, and epicardium. From a very basic consideration, these structures are, therefore, analogous to the intima, media, and adventitia of the arterial system.

Endocardium

The inner lining of the heart consists of a single layer of endothelium supported by a relatively dense connective-tissue zone of collagen, some elastic fibers, and fibroblasts.

Myocardium

The major proportion of the cardiac wall consists of interlacing bundles of striated muscle fibers bound by thin connective-tissue trabeculae that carry the abundant vasculature. These interstitial tissues are more prominent in the auricles where they contain relatively more elastic fibers.

Epicardium

This external covering of the heart consists of a surface monolayer of uniform mesothelial cells which is in continuity with the inner lining of the pericardium. The thin

epicardial membrane is supported on a thin connective-tissue zone containing fine elastic fibers, vessels, and nerves. Near the larger vessels in the sulci and atrioventricular junctions, considerable fat tissue may be added to this subepicardial layer.

Pericardium

Although not an integral component of the heart proper, this very important encasing sac has an inner lining of mesothelial cells, continuous with the epicardium, which is supported on a *lamina densa* of connective tissue (collagen, elastic, and fibrous elements).

CLINICAL SYNDROME

Prior to the past 15 or 20 years, it was traditional to consider the heart as being relatively resistant to the actions of ionizing radiation, particularly in the dose ranges and energy levels customarily used in radiotherapy at that time. Under these circumstances the reaction of the skin and soft tissues of the treatment field generally limited the quantity of radiation that could be used against neoplasias of the thorax.

In spite of this inherent and unintentional protective factor, infrequent, sporadic case reports of cardiac and pericardial damage appeared subsequent to unusually large exposures or repeated exposures to the mediastinal region.

More recently, vastly improved high-energy radiation devices have minimized the limitations previously imposed by the dermal response and have allowed greater latitude in the treatment of deep-seated neoplasms.

However, there has been a disturbing increase in the proportion of treated patients who have exhibited signs and symptoms suggestive of cardiac injury.

This development must be evaluated with a great deal of circumspection. A provisional clinical diagnosis of radiation-induced cardiopathy should be made only on the exclusion of other more likely etiologies:

1. The sequelae of prior intrathoracic surgery.
2. Inflammation of contiguous structures.
3. Infiltration of cardiac or mediastinal tissues by tumor.
4. An autoimmune type of response to the destruction of tumor emboli and implants by radiotherapy or chemotherapy.
5. Exacerbation of preexistent heart disease or the development of cardiac manifestations of systemic disease, such as, for example, a uremic carditis or a septicemia.

Present radiotherapeutic technology has provided certain conditions that have inadvertently affected the possibility of associated radiation-related cardiac injury.

1. Revised dose, dose rate, and fractionation may exceed the tolerance of the heart under specific circumstances.
2. The increased energy transfer at cardiac depth has now shifted to hazardous levels.
3. The enhanced cancericidal potential of megavoltage radiotherapy frequently augmented by more or less effective chemotherapeutic agents permits longer survival, which allows for the development of delayed cardiac pathology.

The clinical syndrome that has been identified with cardiac pathology has been most often associated with the treatment of Hodgkin's disease, in which either the mantle field or a wide mediastinal portal was used. It has also been reported in patients with breast carcinoma where the radiotherapy is particularly directed at the internal mammary lymph-node areas and in carcinoma of the lung, especially where the treatment focuses on the left hilar region and the mediastinum. Reports have also linked this syndrome with therapy of esophageal carcinoma and miscellaneous tumors encountered in the mediastinum.

Although there is a tendency to separate the clinical syndrome into acute and chronic phases, such division is arbitrary at best, and it is likely that the so-called chronic radiation carditis is, in reality, the delayed manifestation of a process that has been developing slowly over an extended period.

The syndrome is most often detected several months after incidental irradiation of the heart with a significant cumulative dose. The following types of response have been reported and may be combined or sequential:

1. No definitive symptomatology but variable pericardial effusion discovered on a routine follow-up roentgenogram.
2. Distinctive chest pains with fever and pericardial friction rub.

The above may exist separately or together and are frequently transient, clearing spontaneously. Uncommonly, these manifestations may progress to the following:

1. Persistent and increasing effusion, which may interfere with the normal contractions of the heart and produce cardiac tamponade. This condition may require repeated pericardiocentesis or the placement of a pericardial window.
2. The development of a constrictive fibrinous and fibrous pericarditis, which can lead to congestive heart failure unless a pericardiectomy is performed.
3. Focal myocardial fibrosis and coronary-artery occlusion have been reported as late consequences of exceptionally large or repeated doses of radiation.

ETIOLOGY OF PERICARDITIS

Many reported causes of pericarditis other than irradiation have been reported:

1. Acute nonspecific pericarditis with chronic constriction.
2. Metastatic tumor.
3. Tuberculosis.
4. Histoplasmosis.
5. Disseminated lupus erythematosus.
6. Rheumatoid disease.
7. Infectious mononucleosis.
8. Trauma.
9. Infection (either primary or by direct extension of inflammatory process from diseased contiguous tissues).

The mechanism of development is obscure. It seems unlikely that irradiation of an assumed normal, relatively avascular mesothelial sac would in itself produce a significant response unless the dose absorbed was inordinately large.

It is far more likely and reasonable to assume that there is a requisite inflammatory or neoplastic condition either of the pericardium itself or in contiguous tissues which initiates this response.

In many cases where constrictive pericarditis has been described in the absence of gross tumor or infection, there have been microfoci of residual tumor cells suggesting a cause—effect relation.

In addition, consideration should be given to the probability that cardiac (specifically pericardial/epicardial) tumor seedings or emboli may have existed prior to therapy and that they played a significant role in the development of the pericarditis even though subsequently destroyed by the radiation. For that matter the products of this tumor-cell destruction per se may initiate the pericardial response. With vastly improved radiation sources and techniques, is it not even more likely that cardiac metastases will be totally decimated, producing tissue changes suggestive of direct myocardial, epicardial, and pericardial damage?

In view of these carcinolytic effects, it is not surprising that cytology examination of the pericardial fluid centrifugate would be negative subsequent to therapy.

It would seem logical to view with suspicion many, or at least some, of those cases of acute pericarditis with effusion in patients who have received only modest amounts of irradiation to the heart region. These may well represent an effect of tumor-cell involvement, even though none of these cells may be found in the surgical or necropsy specimens.

RADIATION HISTOPATHOLOGY (RADIATION CARDIOPATHY)

Although many pathologists are assuming a cautious attitude with regard to the pathogenesis of the cardiac lesions associated with thoracic irradiation, there are those who state, without reservation, that the heart is definitely at risk in the megavoltage therapeutic range and must therefore be considered as a very crucial dose-limiting tissue.

Information regarding the characteristic histologic changes is derived from surgical resections of pericardium and from autopsy materials in those cases where no other etiology is in evidence.

These findings are augmented by the observations of several excellent experimental programs involving a broad spectrum of mammalian species.

A *pericardial effusion* is very often the first detectable manifestation of injury and may become severe enough to require a pericardiocentesis. Unfortunately examination of the aspirated fluid is seldom of value in the determination of the mechanism of formation.

The infrequent identification of unequivocal tumor cells in the centrifugate or the culture of a pathogenic organism can be convincing evidence. On the other hand, the other fluid characteristics, including the presence of blood and a variety of inflammatory cells, are entirely nonspecific.

Pericardium

1. Experimental evidence indicates the microvasculature as being the primary focus of early radiation effect. There is capillary dilatation and congestion followed by endothelial swelling and leakage of plasma fluids into interstitial tissues. This may be accompanied by an infiltration of granulocytes and histiocytes.
2. Also early in the course of the pericardial response the lining mesothelial cells will exhibit swelling and morphology suggesting early degeneration.
3. Increasing pericardial effusion may become apparent.

Comment: The above changes are generally considered transient and reversible and would be unlikely to produce symptoms. In some instances the trauma has been more severe, and a progression of pericardial pathology will ensue.

4. The mesothelial membrane may be denuded and replaced by regenerative and often atypical cells that lack the preirradiation uniformity. Some of these proliferating cells can become entrapped in the organizing exudate and mimic clusters of tumor cells.
5. The pericardium progressively thickens because of interstitial edema, deposition of fibrin with an influx of fibroblasts, and an increase in collagen. The *lamina densa* has been shown to be increased in depth and density.
6. No significant delayed endothelial response has been reported other than sporadic thrombosed and necrotic capillaries. There is some neovascularization of the thickened pericardium with capillary proliferation extending into the organizing exudate.
7. The fibrinous exudate clings tenaciously to the damaged pericardial lining, becomes organized, and is ultimately replaced in part by fibrous adhesions. Eventually the division between organizing exudate and pericardium becomes indistinct and discontinuous.
8. Both exudate and pericardium may be sites of occasional small hemorrhages and deposition of hemosiderin pigment.
9. There is no significant inflammatory infiltrate, although macrophages are very much in evidence.

Epicardium

The changes are essentially identical to those of the pericardium and usually are just as severe.

Myocardium

There has been some contention with regard to the frequency of radiation-induced myocardial pathology and the mechanism of its development.

The striated muscle fibers have no regenerative capabilities and have been categorized as radioresistant. Damage to these cells, from whatever cause, will result in the relatively slow evolution of altered morphology and function, atrophy, and eventual replacement by fibrous scarring.

Since these muscle fibers are unusually active, there is great dependence on adequate blood supply. It is therefore logical to assume that the known radiation-response pattern of the microvasculature may produce a relative tissue ischemia and consequent myocardial fiber damage. For exceptionally high radiation doses, this circulatory compromise can be sufficient to effect permanent structural and functional change.

The observed histopathology has been nonspecific.

1. Microvascular thrombosis and necrosis with occasional microhemorrhages.

2. Progressive degenerative changes in muscle cells with pyknotic or sometimes enlarged and bizarre nuclei, loss of defined striations, discontinuity of contiguous cells, and eventual atrophy and dissolution.

3. Diffuse interstitial fibrosis.

4. No significant inflammatory infiltrate.

Endocardium

In contrast to the intima of the medium and small arteries, which is the endocardial counterpart in the systemic vasculature, the endocardium appears to be relatively unresponsive to radiation or gives that impression because of the large surface area involved and the acknowledged random characteristic of radiation cytopathology.

There have been no incontrovertible reports of direct radiation damage to the endocardium, although it is possible that focal radiation-related fibrosis of the heart wall could include a small circumscribed area of the contiguous endocardium.

REFERENCES

Berdjis, C. C., 1971, Cardiovascular System. Pathology of Irradiation, C. Berdjis (Ed.), The Williams & Wilkins Company, Baltimore, Md.

——, 1960, Cardiovascular System and Radiation. Late Effect of X-Rays on the Arteries of the Adult Rats, *Strahlentherapie*, 112: 595.

Botti, R. E., et al., 1968, Radiation Myocardial Fibrosis Simulating Constrictive Pericarditis. A Review of the Literature and a Case Report, *Cancer*, 22: 1254-1261.

Burch, G. E., R. S. Sohal, S. C. Sun, G. C. Miller, and H. L. Colcolough, 1968, Effects of Radiation on Human Heart, *Arch. Intern. Med.*, 121: 230.

Cohn, K. E., et al., 1967, Radiation Induced Heart Disease, *Radiology*, 89: 302.

Dollinger, M. R., D. M. Lavine, and L. V. Foye, Jr., 1966, Myocardial Infarction Due to Postirradiation Fibrosis of the Coronary Arteries, *J. Amer. Med. Ass.*, 195: 316.

Fajardo, L. F., and J. R. Stewart, 1971, Capillary Injury Preceding Radiation-Induced Myocardial Fibrosis, *Radiology*, **101**: 429-433.

——, and J. R. Stewart, 1970, Experimental Radiation-Induced Heart Disease. Light Microscope Studies, *Amer. J. Pathol.*, 59: 299-315.

——, J. R. Stewart, and K. E. Cohn, 1968, Morphology of Radiation-Induced Heart Disease, *Arch. Pathol.*, 86: 512.

Fanger, H., and C. C. Lushbaugh, 1967, Radiation Death from Cardiovascular Shock Following a Criticality Accident, *Arch. Pathol.*, 83: 446.

Haas, J. M., 1969, Symptomatic Constrictive Pericarditis Developing 45 Years After Radiation Therapy to the Mediastinum. A Review of Radiation Pericarditis, *Amer. Heart J.*, 77: 89-95.

Hurst, D. W., 1959, Radiation Fibrosis of Pericardium with Cardiac Tamponade. Case Report with Post-Mortem Studies and Review of the Literature, *Can. Med. Ass. J.*, 81: 377.

Jones, A., and J. Wedgewood, 1960, Effects of Radiations on the Heart, *Brit. J. Radiol.*, 33: 138.

Kundel, H. L., 1956, The Effect of Gamma Irradiation on the Cardiovascular System of the Rhesus Monkey, *Radiat. Res.*, 27: 406.

Lawson, R. A. M., et al., 1972, Postradiation Pericarditis. Report on Four More Cases with Special Reference to Bronchogenic Carcinoma, *J. Thorac. Cardiovasc. Surg.*, 63: 841-847.

Leach, J. E., and K. Sugiura, 1941, The Effect of High Voltage Roentgen Rays on the Heart of Adult Rats, *Amer. J. Roentgenol.*, 45: 414.

Liebow, A. A., S. Warren, and E. DeCoursey, 1949, Pathology of Atomic Bomb Casualties, *Amer. J. Pathol.*, 25: 853.

Masland, D. S., C. T. Rotz, Jr., and J. H. Harris, Jr., 1968, Postradiation Pericarditis with Chronic Pericardial Effusion, *Ann. Intern. Med.*, 69: 97-102.

Muggia, F. M., and P. A. Cassileth, 1968, Constrictive Pericarditis Following Radiation Therapy, *Amer. J. Med.*, 44: 116-123.

Patek, P. R., 1939, The Morphology of the Lymphatics of the Mammalian Heart, *Amer. J. Anat.*, 64: 203-249.

Phillips, S. J., et al., 1971, Pathologic Sequelae of Acute Cardiac Irradiation in Monkeys, *Amer. Heart J.*, 81: 528-542.

——, J. A. Reid, and R. Rugh, 1964, Electrocardiographic and Pathologic Changes After Cardiac X-Irradiation in Dogs, *Amer. Heart J.*, 68: 524.

Prentice, R. T., 1965, Myocardial Infarction Following Radiation, *Lancet*, 2: 388.

Rubin, E., J. Camara, D. M. Grayzel, and F. G. Zak, 1963, Radiation-Induced Cardiac Fibrosis, *Amer. J. Med.*, 34: 71.

Sams, A., 1965, Histological Changes in the Larger Blood Vessels of the Hind Limb of the Mouse After X-Irradiation, *Int. J. Radiat. Biol.*, 9: 165-174.

Senderoff, E., M. Eaneko, A. R. Beck, and I. E. Baronofsky, 1961, Effects of Irradiation on Normal Canine Heart, *Amer. J. Roentgenol., Radium Ther. Nucl. Med.*, 86: 740.

Smith, D. J., 1961, Effects of Gamma Radiation on Isolated Surviving Arteries and Their Vasa Vasorum, *Amer. J. Physiol.*, 201: 901.

Stewart, J. R., et al., 1971, Dose Response in Human and Experimental Radiation-Induced Heart Disease: Application of the Nominal Standard Dose (NSD) Concept, *Radiology*, 99: 402-408.

——, 1967, Radiation-Induced Heart Disease, *Radiology*, 89: 302.

——, and L. F. Fajardo, 1971, Radiation-Induced Heart Disease, Clinical and Experimental Aspects, *Radiol. Clin. N. Amer.*, 9: 511-531.

——, L. F. Fajardo, K. E. Cohn, and V. Page, 1968, Experimental Radiation-Induced Heart Disease in Rabbits, *Radiology*, 91: 814.

Takaoka, A., H. Kaneda, M. Urano, and S. Kikkawa, 1968, An Electrocardiographic Study of Cardiac Damage Secondary to Radiotherapy of Malignant Intrathoracic Tumors, *Radiol. Clin. Biol.*, 38: 1.

Thibaudeau, A. A., and W. L. Mattick, 1929, Histological Findings in Hearts Which Have Been Exposed to Radiation in the Course of Treatment of Adjacent Organs, *J. Cancer Res.*, **13**: 251.

Vaeth, J. M., L. Z. Feigenbaum, and M. D. Merrill, 1961, Effects of Intensive Radiation on the Human Heart, *Radiology*, 76: 755.

Warren, S., 1942, Effects of Radiation on Normal Tissues. VI. Effects of Radiation on the Cardiovascular System, *Arch. Pathol.*, 34: 1070.

Warthin, A. S., and E. A. Pohle, 1931, The Effect of Roentgen Rays on the Heart. III. The Toleration Dose for the Myocardium of Rats, *Amer. J. Roentgenol.,* 25: 635.

____, and E. A. Pohle, 1929, Effect of Roentgen Rays on Heart: Microscopic Changes in Heart Muscle of Rats and of Rabbits Following Series of Exposures, *Arch. Intern. Med.,* 43: 15.

Fig. 3.1 Radiation cardiopathy. This low-power photomicrograph includes endocardium, myocardium, subepicardial adipose layer, and epicardium. The epicardium is thickened and densely fibrotic, and its surface is coated by fibrin showing some organization. The subepicardial fat is traversed by fibrous trabeculae. The myocardium shows no definite changes that might be ascribed to the irradiation. The epicardial and myocardial vessels have thickened walls. There is no inflammatory infiltrate.

Fig. 3.2 Radiation cardiopathy. In the early stage of the development of epicarditis, there is deposition of fibrin on a thickened epicardium. This exudate will eventually adhere to a similar fibrin layer on the overlying pericardium. These fibrinous adhesions are at first easily lysed by blunt dissection; however, organization of this fibrin bond takes place and results in a tightly constrictive pericarditis. There is no histologic feature of this epicardial response which could be considered as characteristic of irradiation. This nonspecific pericarditis may be found associated with a number of nonradiation-related diseases. Note in this photomicrograph the early organization of the exudate, the irregularity of the epicardial surface, the lack of a significant inflammatory infiltrate, the dilated lymphatic vessels, and the normal structure of the myocardium.

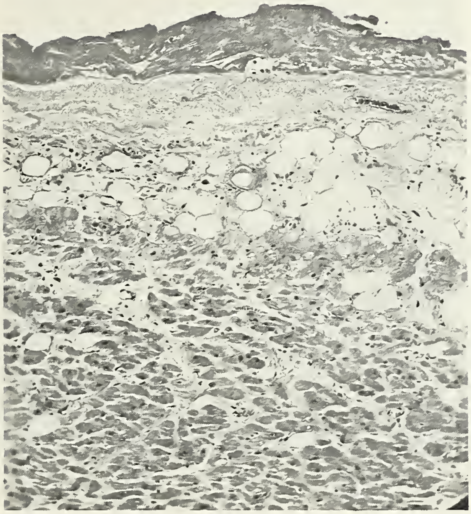


Fig. 3.3 Radiation cardiopathy. The epicardial changes may vary. In this photomicrograph the exudate is a dense fibrinous layer without appreciable organization. The fibrosis of the epicardium has involved to some degree the epicardial adipose tissue. There is no inflammatory reaction. This nonspecific bland cardiac response is associated with extensive irradiation to the mediastinal area with sufficient frequency to suggest an etiologic relation.

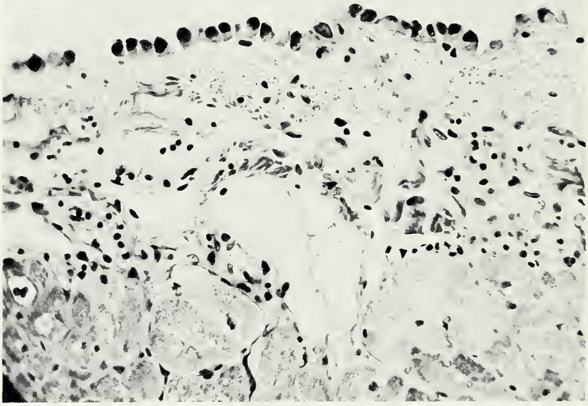


Fig. 3.4 Mesothelial response. The mesothelial membrane that covers the epicardium will react to a variety of stimuli. In this particular case the left anterior ventricle was included in the radiation field, although the amount of radiation is not known. The mesothelial cells are enlarged and somewhat pleomorphic. There is no other epicardial response except dilation of lymphatics.

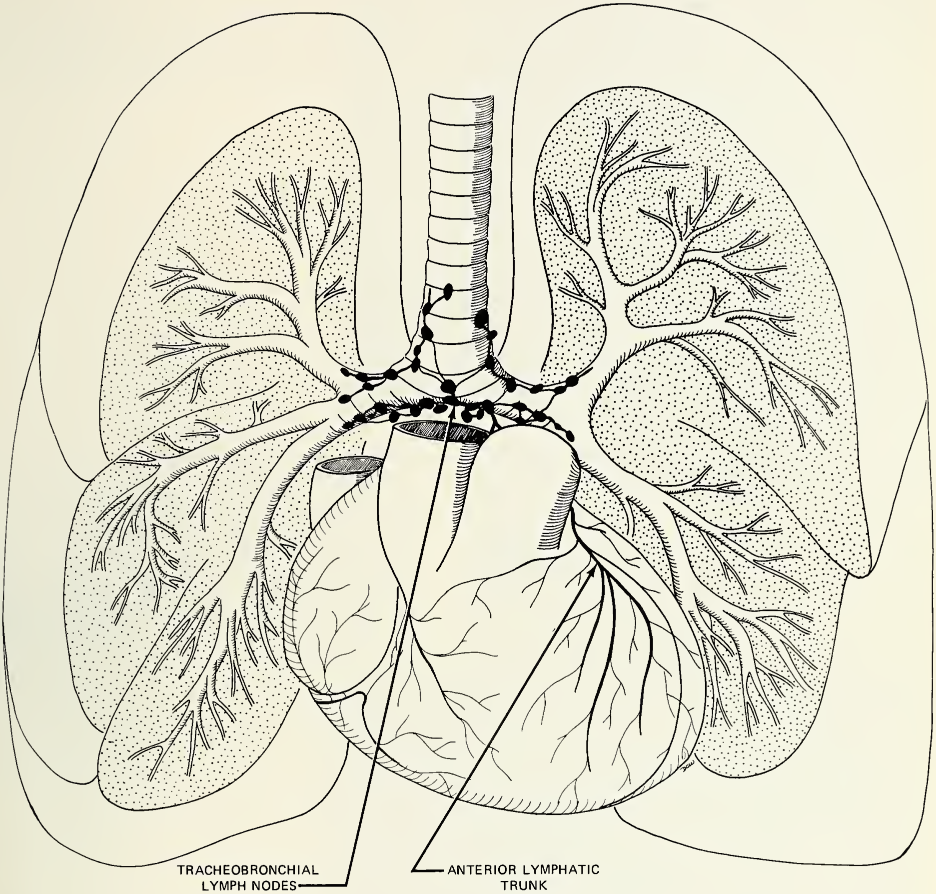
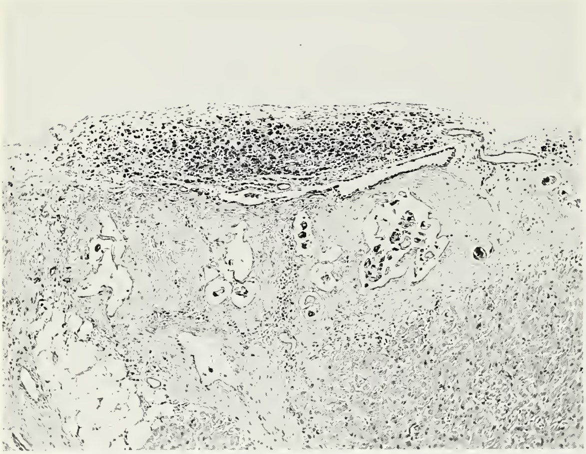


Fig. 3.5 Lymphatics of the heart. This schematic diagram represents a frontal view of the heart and lungs with the pericardium and anterior portion of the lungs removed. The lymphatic drainage of the entire cardiac wall is directed toward the major collecting trunks, which lie in the anterior and posterior longitudinal sulci. These vessels join in the vicinity of the coronary sulcus and pass cephalad behind the pulmonary artery to drain into the tracheobronchial nodes.



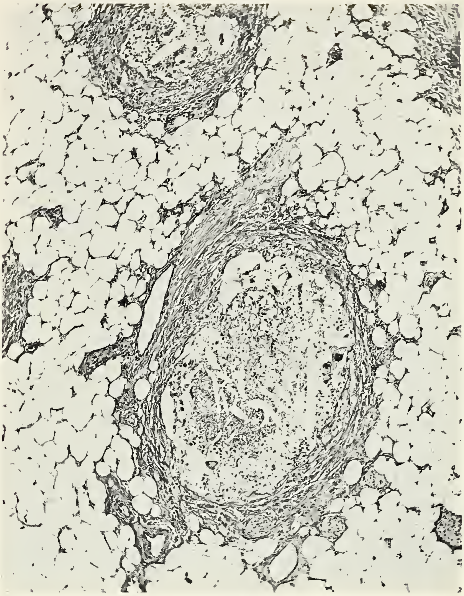
(a)

Fig. 3.6 Irradiation of cardiac tumor emboli. (a) Some cases of cardiac irradiation which subsequently develop signs and symptoms of pericardial and/or myocardial disease may represent responses to degenerative changes in retrograde lymphatic or microvascular tumor emboli and pericardial tumor seeding. This photomicrograph shows a densely fibrotic epicardium with greatly dilated lymphatics containing enlarged and pleomorphic tumor cells damaged by the irradiation. On the epicardial surface is a plaque-like tumor seeding with most of the cells undergoing degeneration. Compare the size of these cells with the smaller and more uniform reactive mesothelial cells lining the cystic structure beneath the implant.

(b)

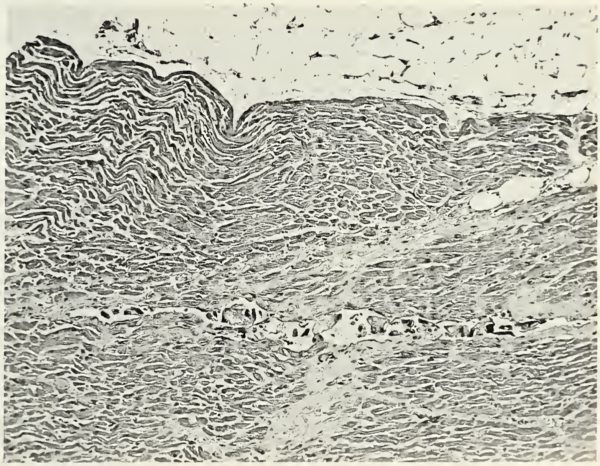
(b) The larger communicating lymphatics between myocardium and epicardium are also dilated and tumor containing. The blood vessels do not appear to be involved in this process, although similar vascular tumor dissemination has been observed in many instances.

(c) In some of these cases, the tumor emboli had established micrometastases in the epicardial tissues and had attained significant size at the time the heart received the irradiation. This photomicrograph illustrates the focal necrotic residue of two such metastases. Note the degenerating tumor cells.



(c)

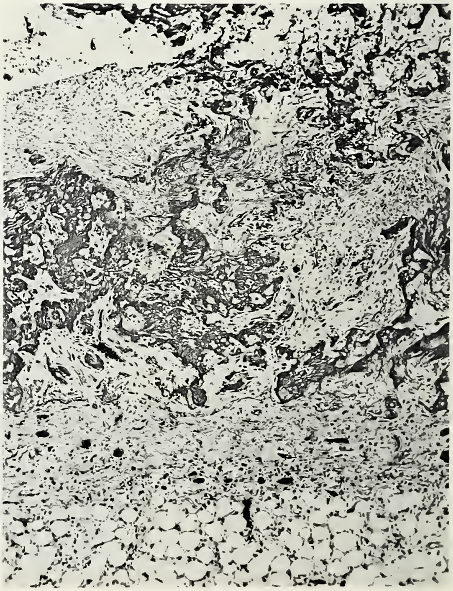
(d) These radiation-altered tumor cells readily become wedged in the lymphatic capillaries, and, although this condition is most often encountered in the epicardium, it can also be observed deep in the myocardium. Some of the myocardial emboli exhibit associated focal fibrosis with little or no inflammatory response. The pathogenesis of this lesion is not understood, although the appearance suggests focal ischemia.



(d)

(a)

Fig. 3.7 Pericarditis and metastases. (a) This individual was diagnosed as having severe pericarditis secondary to intense mediastinal irradiation. In this very-low-power photomicrograph the full thickness of the ventricular wall is shown with the severe fibrinous and fibrous epicardial response.

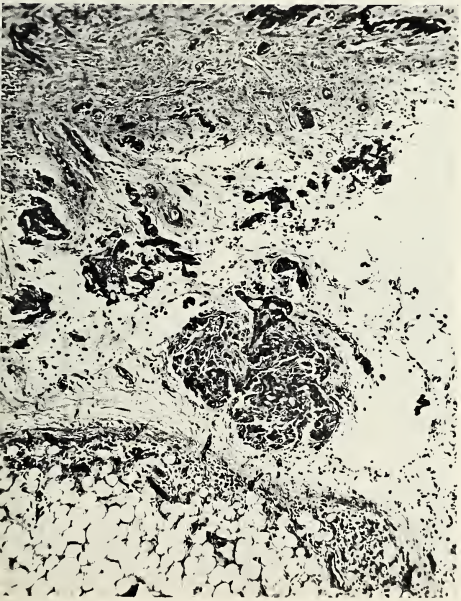


(b)

(b) At high power the composition of this epicardial reaction shows in greater detail the fibroblastic organization of the exudate with irregular islands of dense fibrin remaining. There is considerable invasion of this exudate by newly formed capillaries. The fibrous epicardium and subepicardial adipose tissue are shown at the bottom of this section.

(c) In one area of the exudate were a few entrapped clusters of atypical cells, and some were noted in endothelial-lined spaces of the epicardium.

(c)



(d) The above finding led to the examination of additional heart sections. This photomicrograph shows a large nodule of tumor present on the surface of the epicardium and enclosed by the very thick organizing epicardial exudate. Such association between epicardial tumor emboli and surface implants and concurrent fibrous/fibrinous reaction are more common than previously thought and raise some questions as to the mechanism of formation of some of the so-called radiation pericarditis cases.

(d)

Chapter 4
Lung

NORMAL STRUCTURE AND FUNCTION

Enclosed within the semirigid confines of the thorax are the major components of the cardiorespiratory system. The physical protection afforded by this osseous cage (ribs, sternum, and thoracic vertebrae) and the associated striated muscle and overlying integument belies the vulnerability of these viscera to agents transmitted via inspired air and circulating blood. Particularly susceptible to the actions of physical, chemical, and biological stresses are the lungs since they comprise the terminus for gaseous interchange and a major capillary network in the circulatory system of the body. Of particular note is the frequency with which the lungs are involved directly and indirectly by neoplasia.

The primary functional responsibility of the lung is to efficiently effect gaseous interchange between the environmental atmosphere and the circulating blood while keeping the two media physically separate. For this purpose there are three interacting anatomical and physiological components to the respiratory system.

1. *Air passages:* An arborate pattern of branching airways of diminishing caliber but increasing total cumulative volume and luminal cross section.

2. *Respiratory parenchyma:* Contiguous clusters of distensible thin-wall sacs at the termini of the air passages.

3. *Vascular system:* A fine mesh of interconnecting capillaries which courses through the air-sac walls and is served by an abundantly branching system of arteries and veins.

Air Passages

We are concerned here with those segments of the air-transport system which lie within the thoracic cavity.

TRACHEA AND BRONCHI. These tubular structures, in effect, lie outside the respiratory parenchyma and have no major function other than the transport of air. Their lumens are maintained patent by cartilaginous rings and plates that are present as far distally as the small bronchi but are not normally found in the bronchioles. The number of successive generations of bronchial divisions ranges from 25 for the elongate passages serving the lower lobes to as few as 6 generations going to the respiratory parenchyma adjacent to the main bronchial divisions at the hilus.

The mucosa is lined with a continuous layer of pseudostratified, ciliated, columnar epithelium with frequent interspersed mucin-producing goblet cells. These cells are attached by elongate cytoplasmic extensions to a well-defined basement membrane. Between these attachments are fixed, small, rounded cells that comprise the proliferative compartment of the epithelium. The basement membrane forms a semipermeable barrier between the epithelium and the underlying loose connective tissue of the lamina propria, which contains a network of capillaries and nerve fibers and encircling smooth-muscle fibers. External to the muscle layer and within the cartilage plates is a cuff of connective tissue containing mixed mucous glands that are ducted to the lumen and larger nutritive vessels.

The medium and small bronchi are similar in structure but exhibit fewer epithelial goblet cells and mucous glands. The cartilage plates become smaller and less consistently distributed.

Respiratory Parenchyma

The functional unit of the lung is the pulmonary lobule, which lies entirely within the lung parenchyma and its encasing pleura and consists of the terminal bronchiole and that segment of the respiratory parenchyma which it serves.

The histology of the terminal bronchiole does not differ significantly from that of its larger counterparts and is, in fact, primarily an airway but with no mural cartilage or glands and infrequent goblet cells.

Of some interest is the presence of occasional diverticulations of the mucosa through the underlying connective tissue and smooth-muscle fibers. Under some circumstances these have been observed to link up with contiguous respiratory bronchioles or alveoli and are known as the canals of Lambert. An occasional true alveolus can be seen to bud from the terminal bronchiole.

Each terminal bronchiole divides to form one or more generations of respiratory bronchioles. Because many alveolar ducts and alveoli may arise directly from this airway, the wall is usually discontinuous and difficult to define in the basically two-dimensional microslide preparation. The epithelium is nonciliated, low cuboidal supported

on a fine membrane with underlying strands of smooth muscle and collagen and elastic fibrils. The connective-tissue elements here and in the associated alveolar ducts tend to circumscribe the air sac and duct openings in a purse-string-like manner.

ALVEOLAR DUCT. These irregular spaces form a common vestibule for the clustered alveolar sacs whose ostia comprise essentially the total limits of the alveolar duct. Where there is some semblance of wall, it consists of nubbins and ridges of smooth muscle, collagen, and elastic fibers surmounted by a markedly attenuated epithelial membrane whose individual cells are difficult to delineate by light microscopy.

ALVEOLUS. These thin-walled, irregular, cup-like outpouchings from the acini and alveolar ducts are the functional termini for the gaseous exchange. They comprise about 50% of the total lung volume. It has been estimated that there are approximately 300 million alveoli in the adult human lung which collectively provide a surface area of 70 to 80 m^2 for the effective interchange of gases.

No structural component of the respiratory system has been more controversial than the delicate alveolar septa that separate adjacent air sacs.

The major components of the interalveolar septa are as follows:

1. *Alveolar capillaries:* Most of the septal volume consists of the fine, close mesh of capillaries, which, in effect, makes the endothelial cell the most abundant cell population of the septum. The capillary endothelial cells are supported by a very thin membrane.

2. *Alveolar epithelium:* The alveolar septal surface is covered with a single layer of extremely attenuated epithelial cells that are in continuity with the epithelium of the alveolar ducts and respiratory bronchioles. These cells, the alveolar-lining cells, are so thin that they are very difficult to identify by light microscopy but are readily observed by electron microscopy.

As is true with other surface epithelia, the alveolar lining is a cell-renewal system but with an apparent relatively long turnover time in the unstressed state. Some conjecture continues with regard to the mechanism of cell replenishment, i.e., in situ cell renewal as opposed to proliferation of precursor cells on the alveolar-duct surface and their subsequent surface migration to maintain the integrity of the epithelium.

There are rounded finely granular cells associated with the alveolar epithelium which are considered to be variants of similar derivation. They appear most often near the junction of the alveolus and the alveolar duct. It has been postulated that these cells produce a surface-active monomolecular film that coats the interface between the alveolar air and the lining epithelium.

The alveolar epithelium rests on a delicate basement membrane in a fashion similar to that of the underlying capillary endothelium. From this it can be noted that, over a large proportion of the total alveolar surface, the alveolar air and the circulating blood are separated only by the greatly attenuated cytoplasmic expansions of the epithelial and endothelial cells and their respective basement membranes. The transit distance for gaseous exchange may be 0.20 μm or less.

3. *Septal cells:* Between the limiting epithelia of the septum and the enclosed closely approximated capillaries is a potential interstitial space that is difficult to identify histologically unless an outpouring of edema fluid separates the septal structures.

Within this space is a population of rounded histiocytic cells variously known as septal cells, alveolar interstitial cells, alveolar cells, or alveolar phagocytes.

Their derivation is not fully understood, but two theories are currently popular: (1) that they arise from multipotential septal precursor cells and (2) that they represent the migration of monocytic cells from the blood.

Their phagocytic potential is apparently fully motivated only after these cells have migrated through the septal wall and come to lie free and mobile in the alveolar space. They are thus capable of ingesting both exogenous materials reaching the alveoli via the inspired air and endogenous substances and debris resulting from certain disease states.

Some of these septal cells contain many cytoplasmic lipid droplets and have even been considered to be a conditional sub-type of septal cell. This lipid has been postulated as being derived from the circulating blood. At the same time, these vacuolated cells have a lessened propensity for the phagocytosis of additional materials.

4. *Leukocytes:* Even in the unstressed state, probably there is some degree of diapedesis of circulating leukocytes through the septal capillary wall, into the interstitium, and thence into the alveolar space. This should be considered a transient cell population that may be increased dramatically in many morbid conditions but is minimally present in response to irradiation.

Vascular System

Two separate circulatory patterns supply the lungs, and, since their anatomical relations and functional responsibilities differ, they should be considered individually.

The *pulmonary artery*, arising from the right ventricle of the heart, distributes the blood through its numerous ramifications, coursing peripherally in parallel with the bronchial arborizations. The pulmonary arterioles, as they approach the respiratory parenchyma, give rise to many precapillaries, which, in turn, lead into the rich capillary networks that surround the alveoli.

The entire output of deoxygenated blood from the right ventricle is thus accommodated by this extensive distensible microvascular mesh, enabling the blood to give up its toxic gases in exchange for the oxygen of the inspired air.

Postcapillary venules collect this reoxygenated blood and transport it via the venous counterpart of the pulmonary artery to eventually empty into the left auricle through the pulmonary veins.

Anastomotic shunts between capillaries and arterioles are numerous and provide a mechanism for the redirecting of the pulmonary flow in the event of segmental obstruction.

The *bronchial artery* arises from the thoracic aorta, and its branches supply the bronchi, the interlobular supportive stroma and pleura, and the vasa vasorum of the pulmonary arterial tree.

Anatomically the bronchial arteries can be differentiated from the branches of the pulmonary artery in that they are usually positioned in the peribronchial connective tissue near the cartilage plates and associated with nerve bundles. The caliber of the bronchial artery at any given site is usually somewhat smaller than its pulmonary-artery counterpart.

No review of the vascular systems of the lung would be complete without consideration of the lymphatic pattern. Two lymphatic networks, deep and superficial, serve the lungs and drain centripetally to the hilus. The only exception to this is in the subpleural zone where at times there is free anastomosis between the two plexi and the flow can be initially outward toward the pleural network.

The deep system, which anatomically parallels the pulmonary vascular tree, appears to have its origin in blind channels situated as far peripherally as the respiratory bronchioles and alveolar ducts. The lymph flow is apparently stimulated by the respiratory movements.

As the deep and superficial lymphatics course toward the hilus, they are joined by additional peribronchial, perivascular, and perineural lymphatics, ultimately draining into the hilar lymph-node group.

Although the lung is well barricaded against external agents by its position within the thoracic cage and buffered against excessive physiological stresses by efficient biological safeguards, it is relatively easy to upset the delicate functional balance of this critical body system.

1. Changing the composition (and temperature) of the external atmosphere (inspired air).
2. Impeding the inflow of air, usually by a physical obstruction of the air passages.
3. Blocking the conversion and carrying capacity of the receptor erythrocytes.
4. Altering the circulation of blood through the respiratory parenchyma.
5. Inhibiting respiration by decreasing the air-containing lung volume and its expansile propensity.
6. Obstructing or retarding the gaseous interchange in the alveoli.

The last three factors generally become operative when there is damage to the parenchyma of the lung regardless of etiology. This is the area that is most vulnerable to the injuries induced by the direct action of ionizing radiation.

CLINICAL SYNDROME

As is true of almost all tissues lying within a radiation-therapy field, there is no reliable means of determining a reasonable estimate of the incidence of radiation injury in the lung.

If minimal clinical respiratory or radiographic criteria are established, then some indication of the frequency of the clinical syndrome can be determined. It is probably reasonable to assume that about 10 to 20% of those individuals receiving cancericidal doses to the thoracic region will develop a detectable presumptive syndrome. This figure would be much higher if there were means for safely and easily performing a histologic examination.

What is surprising is that, even with increased emphasis on the evaluation of this sequela and the various means that have been devised to offset this complication, the incidence has not changed appreciably, and there is, in fact, relatively little known about the fundamental pathogenesis of this complication.

Without consideration of the pathologic condition that predicated the use of radiation therapy, it must be assumed that a large proportion of treated individuals develop a transient radiation pneumonitis that is either symptomatically silent or not recognized as to its true genesis. Many of these might show some radiographic evidence if films were routinely made. Several physiological tests have been applied to follow the development and progression of the pulmonary radiation changes in man, but none has been shown to be any more sensitive or reliable than the careful radiographic examination of the lung fields. Here, as with the clinical signs and symptoms, the findings become characteristic but not specific.

Within several months of the initial exposure, and generally in the first to third months, there may be lung changes by roentgenogram. McIntosh and Spitz [*Amer. J. Roentgenol., Radium Ther. Nucl. Med.*, **41**: 605-615 (1939)] felt that they could separate this response into four grades of severity:

Grade 1: Increase in bronchovascular markings. Slightly decreased aeration over the treated areas. General homogeneous haze (? pleural reaction).

Grade 2: Either or both the above plus small irregular but discrete patches of peribronchial consolidation.

Grade 3: Confluent areas of exudation with retraction of the mediastinum to the affected side. Elevation of the diaphragm.

Grade 4: Extensive confluent exudative area with marked contraction of the lung producing dense consolidation of the treated area.

The first two grades are transient and reversible and may very likely be symptomless. Individuals having the more severe forms with greater volumes of lung involved may develop slight to moderate fever, a persistent hacking cough, which is at first dry and then productive of a diffusely pink or reddish sputum, and variable dyspnea (particularly on exertion). Chest pain has been only rarely noted. Those in the latter categories are subject to severe respiratory distress and high fevers with subsequent possibility of cor pulmonale and right heart failure.

Although the vast majority of those developing radiation pneumonitis will fall into these categories, there are those few who respond more dramatically and, unfortunately, with greater morbidity. Occasionally a patient will rapidly lapse into marked cardiorespiratory distress even while undergoing therapy, and often heroic measures are required to maintain life through the critical period of resolution and resorption of the acute exudative phenomenon. Still others will tolerate the therapy well during the early posttreatment phase only to become severely

debilitated or die as a result of the delayed extensive and permanent fibrosis of the respiratory parenchyma.

RADIATION HISTOPATHOLOGY (RADIATION PNEUMONOPATHIES)

Clinically significant reactions of the lung to radiation can be arbitrarily classified into two stages that are not necessarily directly interrelated. *Radiation pneumonitis,* or the more descriptive term *early exudative radiation pneumonopathy,* represents the early response that usually develops within 6 months of the initiation of radiation therapy and in most instances is largely a reversible tissue effect. *Radiation pulmonary fibrosis,* which is the delayed response, becomes manifest anytime from several months to several years after the therapy and is often a progressive debilitating disease.

Radiation Pneumonitis

Probably most (if not all) individuals receiving "standard" tumoricidal radiotherapy, which includes any portion of the lung within the treatment field, will develop an early response to radiation.

If the criteria for radiation pneumonitis include histopathology as well as clinical and radiographic findings, the severity of this response can be arbitrarily classified.

1. *Asymptomatic:* (a) No radiographic change, minimal transient cytopathology and (b) equivocal or slight radiographic alterations reflecting more diffuse histopathology involving clusters of respiratory units in the radiation field.

2. *Minimal transient symptoms (slight cough, sensation of fullness in chest);* characteristic radiograph (linear density and focal consolidation limited to the field of radiation), the pathology will be characteristic:

a. Swelling and degeneration of alveolar-lining cells and septal capillary endothelium.
b. Extravasation of protein-rich edema fluid into septal interstices and into alveolar space as a consequence of item a (above).
c. Activation and proliferation of septal cells that migrate into alveolus and become phagocytic.
d. Lack of inflammatory infiltrate.

All these effects (clinical, radiological, and pathological) are potentially reparable and wholly reversible.

If they are of mild degree, these cases of radiation pneumonitis may not be correctly diagnosed, and the signs and symptoms are often ascribed to other causes.

3. *Characteristic symptomatology (nonproductive hacking cough, variable spiking fever, and shortness of breath that may become severe enough to produce respiratory distress),* radiography of the chest will show marked linear density and consolidation still largely limited to the irradiated area. Pleural effusion is occasionally seen; the pathologic changes are diffuse and marked, although, like the radiographic findings, they are mainly limited to the radiation field:

a. Occlusion of alveolar ducts and alveoli by exudate, which may become compacted against the alveolar walls (hyaline membrane).
b. Greatly enlarged, pleomorphic alveolar-lining cells may lose their cohesion to the basement membrane and lie free within the alveolar space or become incorporated into the hyaline membrane. Some of this fibrin-rich exudate and cell debris may be expelled in the sputum.
c. The denuded surface may exhibit regenerating alveolar-lining cells, usually forming a single layer of cuboidal cells.
d. Variable numbers of alveolar macrophages (mobilized septal cells) act to scavenge the alveoli and are subsequently eliminated via the air passages. Some may find their way into the lymphatics to be filtered through the hilar nodes.
e. Obstruction of septal capillaries by detached degenerative endothelial cells and fibrin thrombi. Some hyaline/fibrinoid thickening of arteriolar walls.
f. Edematous alveolar septa exhibit proliferation of collagen microfibrils and fibrin mesh.

These effects may (1) clear spontaneously, although with this degree of damage it is unlikely; (2) persist for long periods but with gradual regression to a state of lessened tissue compromise; (3) persist for long periods to be supplanted by, or merge into, the picture of pulmonary fibrosis; and (4) weaken the cardiorespiratory reserve and increase susceptibility to intercurrent stress, especially infection.

Radiation Pulmonary Fibrosis

This condition may seemingly arise de novo in an irradiated lung that either has had no clinical or radiographic evidence of pneumonitis during or shortly after therapy or exhibited findings consistent with radiation pneumonitis which spontaneously cleared.

It may also develop in continuity with clinical or radiographic pneumonitis as a progressive densification of the lung associated with a variable respiratory decrement, or there may be a plateau of pulmonary damage which persists for months or even years before increasing fibrosis again becomes evident.

Respiratory difficulty developing in an irradiated lung which has previously been structurally and functionally unimpaired or which has attained a relatively static condition of variable residual injury must receive cautious evaluation. Differentiation must be made between radiation pulmonary fibrosis and recurrence of neoplasia, an exogenous biological infection, a chemical inflammatory process, or an endogenous or idiopathic pulmonary disease state. Additional diagnostic difficulty may be encountered in that two or more of the above morbid conditions can exist coincidentally, and each may predispose the development of precipitate pulmonary infection on the basis of stasis or tissue breakdown.

Most of the histopathologic effects observed in delayed radiation pneumonopathy are related either to the interstitial fibrosis initiated during the treatment and early posttreatment period or to the vascular sclerosis that is characteristic of the late radiation picture in almost all tissues.

1. *Fibrosis:* The progressive interstitial fibrosis results in broadening of the interalveolar septa. The microvasculature becomes encased in this process or crowded into a subepithelial position, and eventually the vessel lumens are obliterated by compression or thromboses. In time the overwhelming nature of this fibrosis produces marked diminution of alveolar air volume and loss of the expansile propensities of the respiratory parenchyma.

2. *Vascular sclerosis:* There is a progressive sclerosis of all vascular elements, but this is especially evident in medium and small arteries and arterioles. The process appears to be a combination of endothelial proliferation, intimal and medial fibrinoid and hyaline degeneration and fibrosis, and variable adventitial fibrosis. These effects are irregularly and discontinuously distributed along the vessels in random fashion. Continued narrowing of the vascular lumens stimulates the development of collateral circulatory channels; however, the degree of ischemia promotes further fibrosis and may become severe enough to produce tissue necrosis.

These delayed effects are most severe in the area subtended by the radiation treatment field. The severity of the secondary fibrosis, however, is largely predicated upon the relative circulatory compromise. The vessels sclerosed by the radiation often service parenchyma well away from the radiation field, thus producing a variable pattern of pulmonary fibrosis not sharply restricted to the irradiated volume. It is not uncommon to observe prominent changes limited by interlobular septa as a result of the segmental deployment of these vessels.

As the severity of this delayed pulmonary fibrosis increases, the potential hazard to the health and life of the irradiated individual becomes of significant concern.

The following late complications are particularly noteworthy:

1. The affected lung becomes contracted, fibrotic, and virtually afunctional.
2. The resulting stasis produces a perfect culture medium for pathogens.
3. Chronic bronchitis, bronchiectasis, and pneumonia are prone to develop.
4. Vessel changes provide a potential source of vascular thrombi.
5. The fibrosed lung is a constant focus of severe and unrelenting patient discomfort.
6. There is undue stress on the cardiorespiratory reserve.

REFERENCES

Adamson, Ian Y. R., D. H. Bowden, and J. P. Wyatt, 1970, A Pathway to Pulmonary Fibrosis: an Ultrastructural Study of Mouse and Rat Following Radiation to the Whole Body and Hemithorax, *Amer. J. Pathol.*, 58: 481-487.

Bate, D., and R. J. Guttman, 1957, Changes in Lung and Pleura Following 2 MeV Therapy for Cancer of the Breast, *Radiology*, 69: 372-386.

Bennett, D. E., R. R. Million, and L. V. Ackerman, 1969, Bilateral Radiation Pneumonitis, a Complication of the Radiotherapy of Bronchogenic Carcinoma, *Cancer*, 23: 1001-1018.

Bertalanffy, F. D., and C. P. Leblond, 1953, The Continuous Renewal of the Two Types of Alveolar Cells in the Lung of the Rat, *Anat. Rec.*, 115: 515.

Boushy, S. F., A. H. Helgason, and L. B. North, 1970, The Effect of Radiation on the Lung and Bronchial Tree, *Amer. J. Roentgenol., Radium Ther. Nucl. Med.*, 108: 284-292.

Bowden, S. F., et al., 1969, Origin of the Lung Macrophage. Evidence Derived from Radiation Injury, *Arch. Pathol.*, 88: 540-546.

Desjardins, A. W., 1932, Action of Roentgen Rays and Radium on the Heart and Lungs, *Amer. J. Roentgenol., Radium Ther. Nucl. Med.*, 28: 701-720.

Engel, S., 1964, Comparative Anatomy and Pulmonary Air-Cleansing Mechanisms in Man and in Certain Experimental Animals, *Health Phys.*, 10: 967-971.

Fleming, W. H., et al., 1960, Hyaline Membrane Following Total Body Radiation: Relation to Lung Plasminogen Activator, *Lancet*, 2: 1010-1011.

Gillam, P. M. S., et al., 1964, Chronic Bronchitis and Radiotherapy of the Lung, *Lancet*, 1: 1245-1248.

Goldenberg, V. E., et al., 1968, Radiation Pneumonitis in Single and Parabiotic Rats. I. Short Term Effects of Supralethal Total Body Irradiation, *Lab. Invest.*, 18: 215-226.

Hoffbrand, B. I., et al., 1965, Effect of Chronic Bronchitis on Changes in Pulmonary Function Caused by Irradiation of the Lungs, *Thorax*, 20: 303-308.

Jennings, F. L., and A. Arden, 1962, Development of Radiation Pneumonitis; Time and Dose Factors, *Arch. Pathol.*, 74: 351-360.

——, and A. Arden, 1961, Development of Experimental Radiation Pneumonitis, *Arch. Pathol.*, 71: 437-446.

Johnson, P. M., R. H. Sagerman, and C. S. Dombrowski, 1970, Ischemia of the Lung due to Ionizing Radiation: Quantitative Studies, *J. Nucl. Med.*, 11: 491-495.

Lichtenstein, H., 1960, X-Ray Diagnosis of Radiation Injuries of the Lung, *Dis. Chest*, 38: 294-297.

McIntosh, H. C., 1934, Changes in the Lungs and Pleura Following Roentgen Treatment of Cancer of the Breast by Prolonged Fractional Method, *Radiology*, 23: 558-566.

Phillips, T. L., 1966, An Ultrastructural Study of the Development of Radiation Injury in the Lung, *Radiology*, 87: 49-54.

Smith, J. C., 1963, Radiation Pneumonitis, *Amer. Rev. Respirat. Dis.*, 87: 647-655.

Stevens, W. E., 1963, Radiation Therapy in Lung Cancer, *Geriatrics*, 20: 816-834.

Warren, S., and J. Spencer, 1940, Radiation Reaction in the Lung, *Amer. J. Roentgenol., Radium Ther. Nucl. Med.*, 43: 682.

Whitfield, A. G. W., et al., 1963, Radiation Damage to Thoracic Tissues, *Thorax*, 18: 371-380.

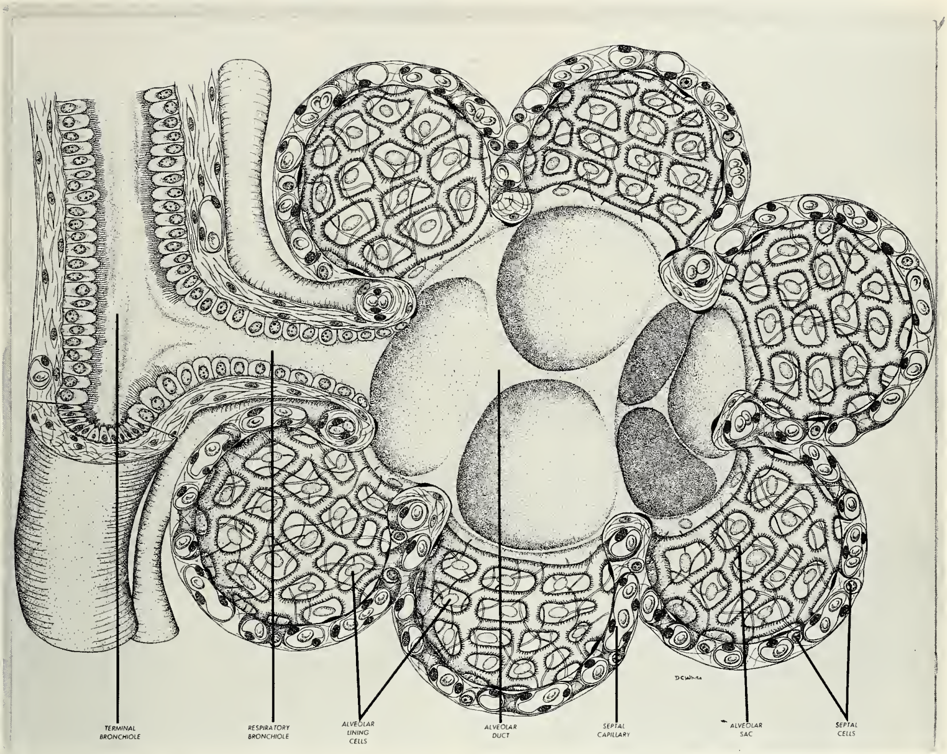
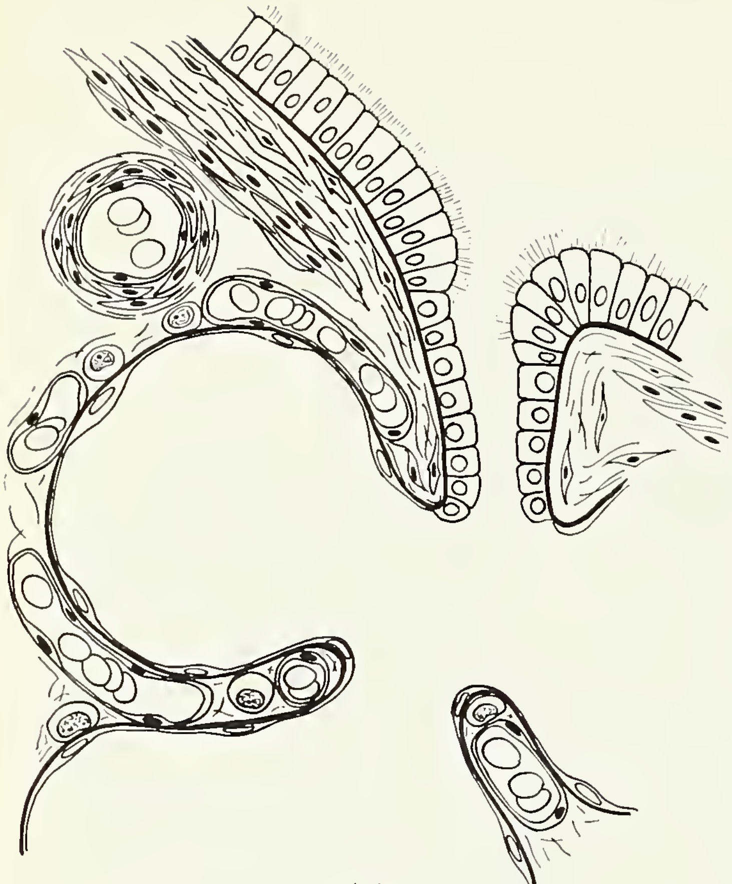


Fig. 4.1 **Normal respiratory parenchyma.** This diagram represents a cross-sectional view into an alveolar duct with its cluster of alveolar sacs. Its continuity with the respiratory bronchiole and larger terminal bronchiole is also shown. The delicate alveolar septa are largely composed of an abundant intercommunicating network of capillaries. Entwining about this microvascular system is a fine mesh of reticulin fibers. A few septal cells are present within the interstitial space. Where the alveolar ostia open into the duct vestibule, the interstitium expands to accommodate a pattern of collagen and elastic fibers and a few smooth-muscle cells. The alveoli are lined by a single layer of very flattened epithelial cells.



(a)

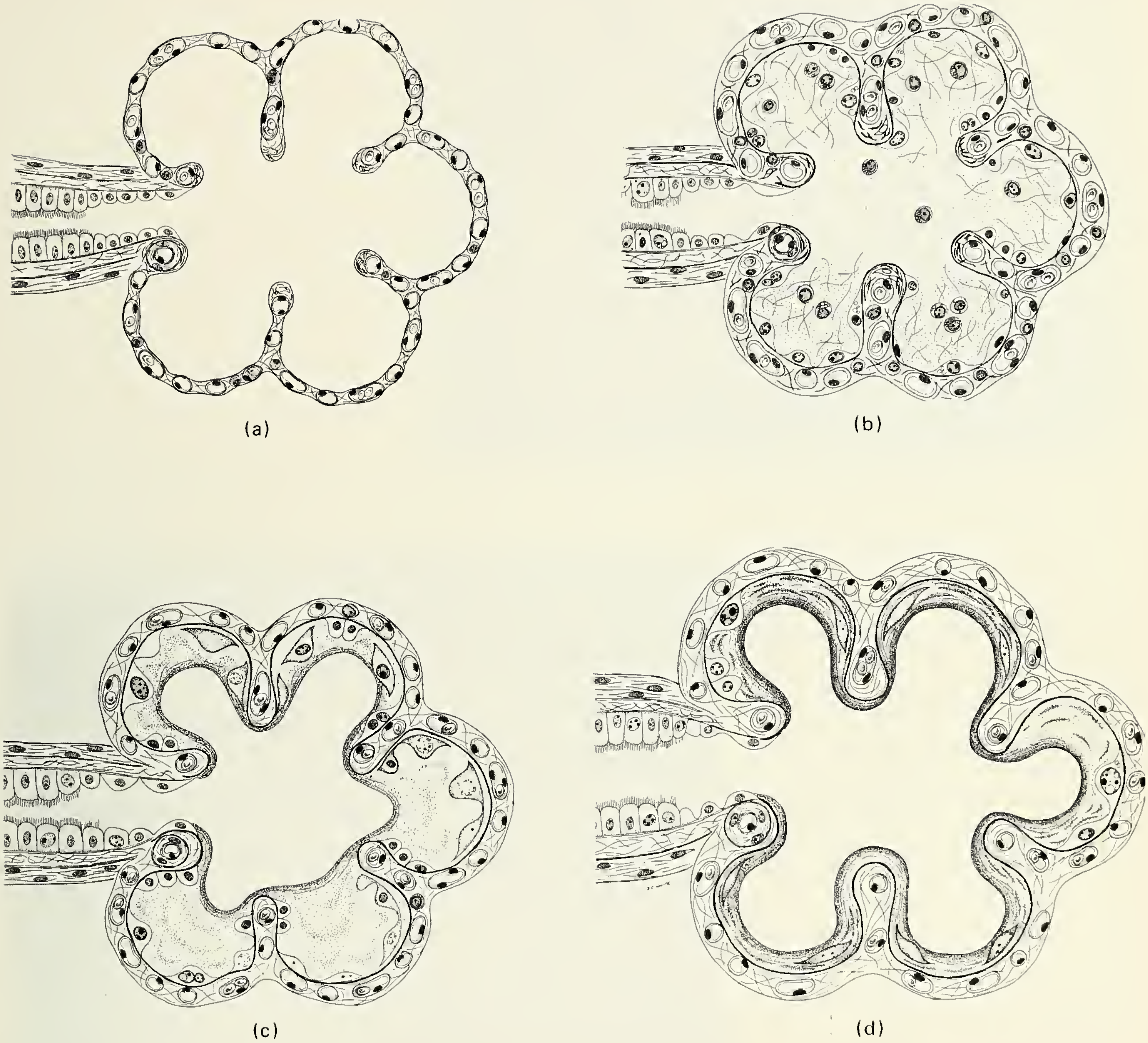
(b)

(c)

Fig. 4.2 Sequential radiation pneumonopathy. **(a)** This diagram represents that portion of a respiratory unit which includes the proximal wall of the terminal bronchiole, a short respiratory bronchiole, an alveolus, and part of the alveolar duct.

(b) The early response is, in part, an exudative one with compromise of the endothelial barrier and outpouring of fluid into the interstitium and then out into the alveolar space. The septal cells are mobilized and migrate through the septal membrane into the alveolar space where they are phagocytic. The connective-tissue elements of the interstitium are increased. The alveolar-lining cells become greatly enlarged with usually proportionate increase in nuclear and cytoplasmic volume. The cells of the bronchiolar epithelium exhibit variable pleomorphism and some loss of cilia in the terminal bronchiole.

(c) The delayed response is primarily one of progressive interstitial fibrosis and associated vascular sclerosis. The small arteries and arterioles show the greatest thickening with concomitant constriction of the lumens. The microvasculature of the alveolar septa is greatly diminished, and the distance between the capillary blood flow and alveolar air is increased manyfold by the interstitial fibrosis. A few enlarged alveolar-lining cells may remain, but most of the septa are resurfaced by cell regeneration. The epithelium of the bronchiole may be metaplastic and hyperplastic.



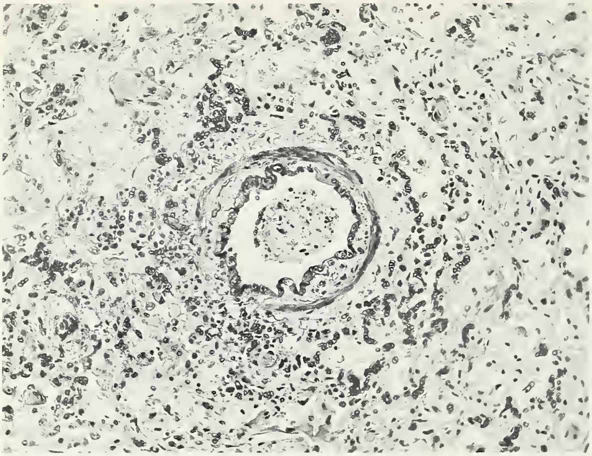
(a) (b) (c) (d)

Fig. 4.3 **Hyaline-membrane formation.** (a) Cross-sectional diagram of preirradiation respiratory unit.

(b) During the early exudative "pneumonitis," large amounts of protein-rich fluid emanate from the damaged septal capillary bed, expand the septa, and pour into the alveolar space and duct vestibule. A mesh of fibrin strands may develop.

(c) Inspired air begins to compress this exudate. Most of the enlarged alveolar-lining cells become detached from the alveolar membrane and lie free within this thickening exudate.

(d) The exudate finally becomes compacted against the alveolar walls, incorporating the denuded and degenerating alveolar-lining cells in the process. This membrane is eventually lysed and absorbed but, while present, virtually precludes any gaseous interchange.



(a)

(b)

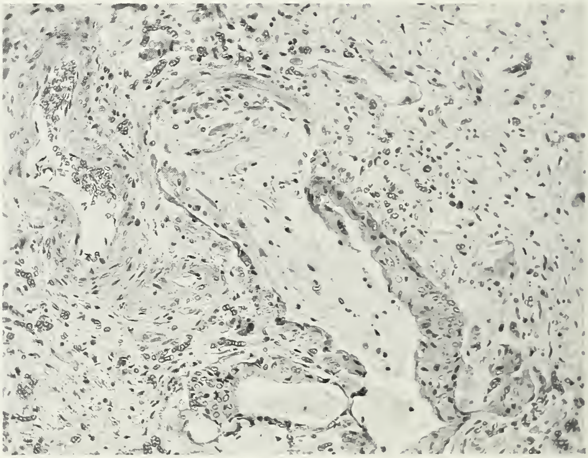
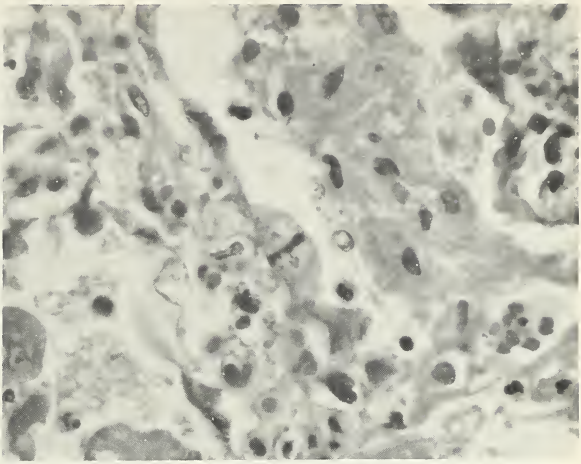
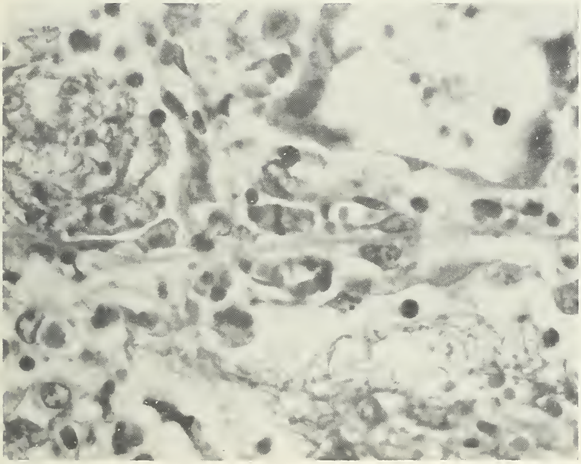


Fig. 4.4 Early exudative phase. **(a)** The alveolar septa and peribronchial tissues are edematous and the microvasculature is congested. Most of the alveolar-lining cells are swollen, and some have already separated from the basement membrane. The alveoli contain exudate and mobilized septal cells (alveolar macrophages) in addition to the sloughed lining cells. The epithelium of the bronchiole in the center of this photomicrograph shows marked cell pleomorphism. The lumen contains exudate, mucin, and cell debris.

(b) This bronchiole exhibits partial mucosal denudation and epithelial metaplasia. The simple, ciliated, columnar epithelium has been replaced by hyperplastic ovoid and squamous cells. The lumen contains a plug of mucin with admixed cell debris. The vessels do not yet show any appreciable thickening of their walls.

(a)





(b)

Fig. 4.5 Cell proliferation in the early response. (a) This photomicrograph illustrates an edematous interalveolar septum with both alveolar surfaces lined with enlarged and pleomorphic alveolar-lining cells. One of the alveolar-lining cells contains a well-defined mitotic spindle (metaphase). There is a dense exudate in the alveolar space. Note the increase of connective-tissue fibers in the septum.

(b) The septal cells, on demand, are also capable of exaggerated proliferation. This photomicrograph shows the juncture of expanded, edematous interalveolar septa. The three alveolar sacs visible here are lined with enlarged pleomorphic alveolar-lining cells and contain exudate with fibrin strands and alveolar macrophages. In the center of this photomicrograph is a dividing septal cell in metaphase. These cells will migrate through the septal membrane and lining epithelium to become the alveolar macrophages.

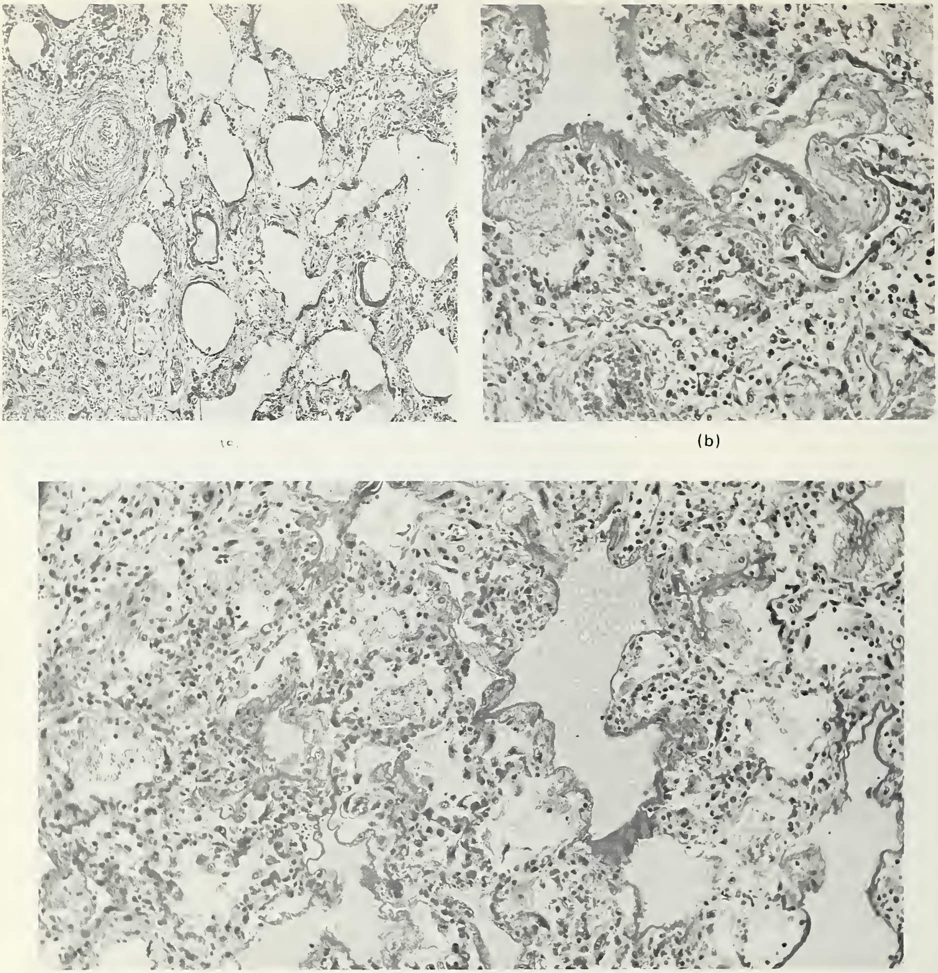
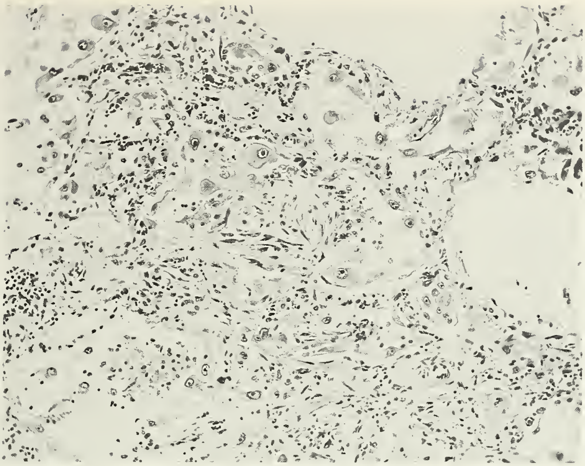


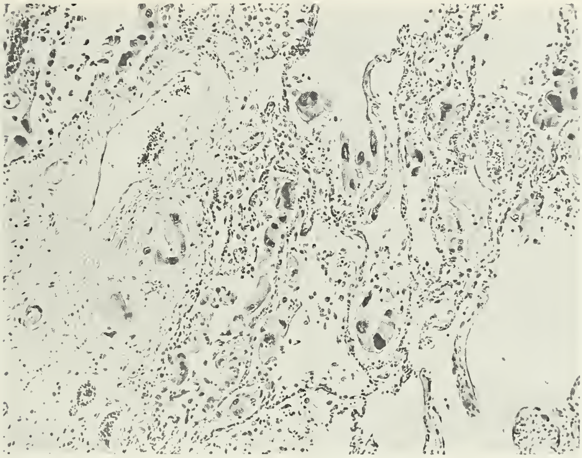
Fig. 4.6 Hyaline-membrane development. **(a)** Hyaline membrane is associated with a diversity of diseases and is encountered with sufficient frequency in radiation pneumonopathy to be considered one of the characteristic responses. This condition has as its early phase the outpouring into the alveolar sacs and alveolar ducts of a fibrin-rich exudate that at first shows focal areas of compression and increased density as seen in this photomicrograph.

(b) This higher power photomicrograph shows the invagination of the membrane into the individual alveolar sacs. The membrane frequently has a layered appearance and tends to incorporate macrophages and sloughed alveolar-lining cells as it becomes molded against the septal surface. Note from the edematous loose texture of the interstitium that this hyaline membrane is characteristic of the early exudative radiation response.

(c) As the development of the hyaline membrane proceeds, the alveolar ducts become expanded by the exudate. The protein-rich substance is compacted against the duct walls and out into the alveoli. Some alveolar sacs become isolated by a bridging of their ostia with the forming membrane. In this photomicrograph it can be seen that this is not always a diffuse process, and many respiratory units do not appear to participate.



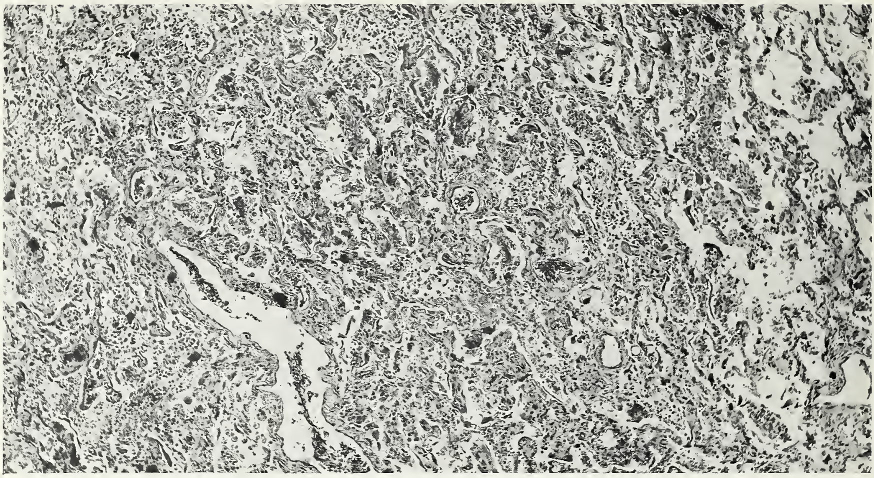
(a)



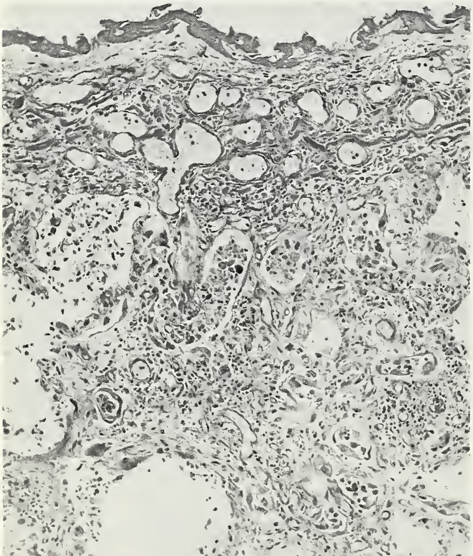
(b)

Fig. 4.7 Comparison of irradiated alveolar-lining cell and irradiated carcinoma. (a) Enlarged and pleomorphic alveolar-lining cells can develop during radiotherapy and the early posttreatment period. There is a proportionate increase in both nuclear and cytoplasmic volumes. The nuclei frequently display hyperchromatism as well as irregular clumping of chromatin. Binucleation and multinucleation are not uncommon, although the total nuclear mass does not seem to increase disproportionately. The cytoplasm may be homogeneous, granular, or vacuolated. These altered alveolar-lining cells may persist for many weeks and months, although they are continually replaced by regenerating epithelium.

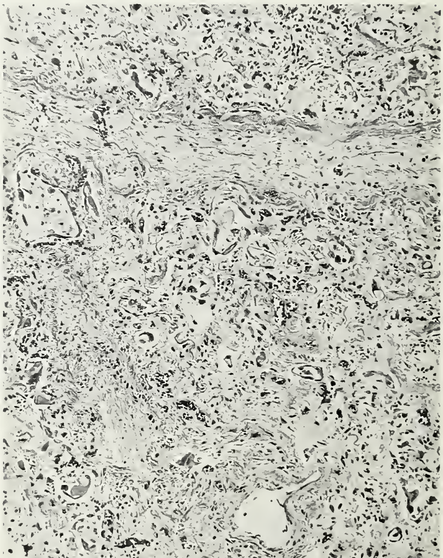
(b) This photomicrograph shows very large and pleomorphic cells discontinuously lining some alveoli. Differentiation from the enlarged alveolar-lining cell is often based on subtle dissimilarities. The nuclear/cytoplasmic ratio is generally significantly greater than that of the alveolar-lining cells. The very large and unusually bizarre nuclei are often intensely hyperchromatic. Irradiation is capable of ballooning some tumor cells to immense proportions. In this section the presence of these cells in vascular channels is convincing evidence of their malignant nature. It should be emphasized that the septal fibrosis, vascular sclerosis, and epithelial changes of radiation pneumonopathy may coexist with residual tumor.



(a)



(b)

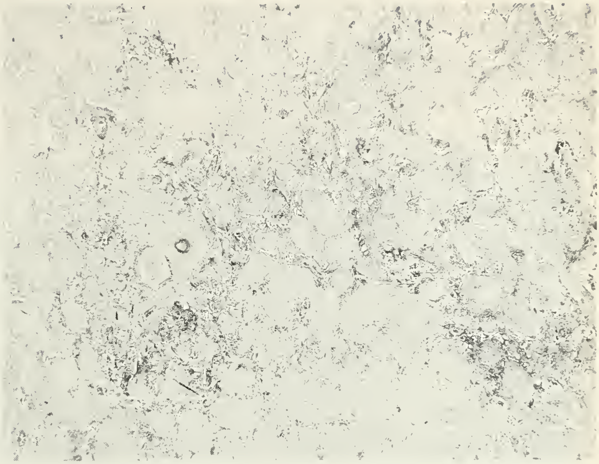


(c)

Fig. 4.8 Early radiation pulmonary fibrosis. **(a)** This low-power photomicrograph shows a diffuse moderate septal fibrosis. Vascular changes have not as yet achieved prominence. Most of the alveoli and alveolar ducts contain macrophages, cell debris, and detached alveolar-lining cells.

(b) The pleura of the irradiated lung may be thickened and fibrotic. The pleural vessels in this section are dilated and congested. There is a thin fibrinous pleuritis present.

(c) In similar fashion the interlobar fissures may be broad and fibrosed. Perivascular and peribronchial zones may be widened by connective-tissue proliferation.



(a)

(b)

Fig. 4.9 Intercurrent pneumonia. (a) It is not uncommon for a relatively mild radiation pneumonitis to rapidly worsen clinically with high fever and acute respiratory distress. The etiology is often a superimposed pneumonia (viral or bacterial). This low-power photomicrograph shows severe, diffuse, organized pneumonia developing in an individual with moderate radiation pneumonopathy. The solid appearance of the pulmonary parenchyma can be readily appreciated.

(b) At higher power the masses of organized, fibrosed exudate are seen occluding the alveoli and alveolar ducts. A moderate septal fibrosis is evident, and some of the lining cells are large and atypical.

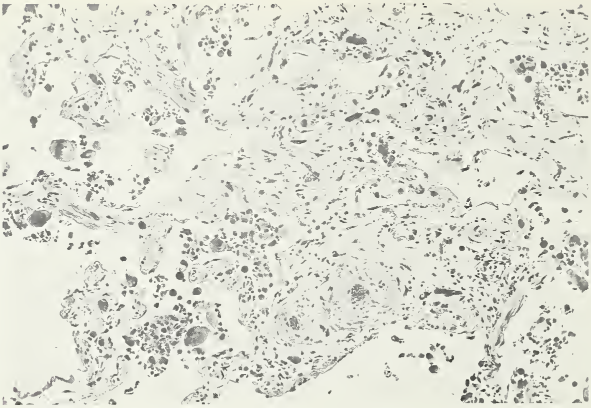


Fig. 4.10 Radiation pulmonary fibrosis. Late delayed radiation pneumonopathies have a tendency to eventually stabilize at some level of tissue damage and functional decrement. The degree of pathology is determined by many interacting factors. In this photomicrograph the basic septal pattern is present; however, interstitial fibrosis is severe. Distorted alveolar-lining cells are still present, and there are macrophages in the air spaces. The medium-size vessels have greatly thickened walls, and the septal microvasculature is markedly diminished.

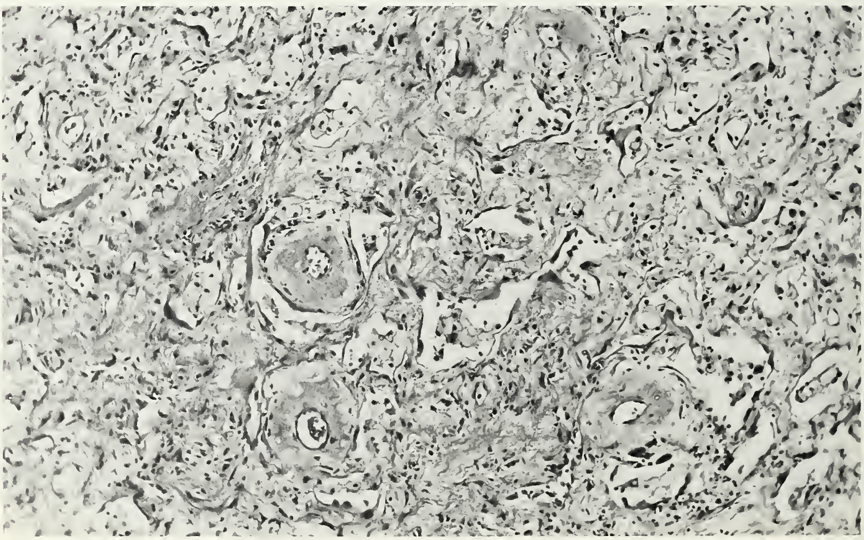
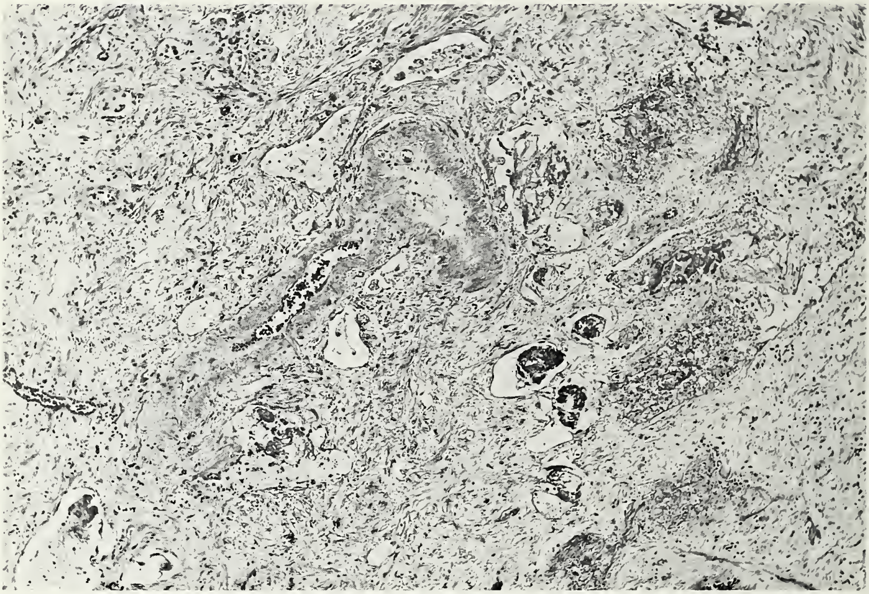


Fig. 4.11 Radiation pulmonary fibrosis. Although the potential air space has been greatly reduced and the septal pattern largely obscured, the connective-tissue proliferation is still in a loose, almost mesenchymal, state. The constricted air spaces are lined with atypical epithelium and contain clusters of foamy macrophages. Vessels are prominent owing to a marked fibrinoid proliferation in the subendothelial and myothelial zones.

(a)

Fig. 4.12 Radiation pulmonary fibrosis. (a) This low-power photomicrograph shows a medium-sized artery as it traverses the severely fibrosed lung parenchyma. Of particular interest is the variable thickness of the vessel wall along its course. In some locations this wall is of essentially normal thickness, and within a few microns it may increase several magnitudes in depth as a result of focal fibrinoid or hyaline change. Moreover, this change may be eccentric with regard to the lumen. In this section the arterial lumen has an essentially uniform caliber; however, many such vessels will have foci of partial to total occlusion.

(Figure continues on following page.)



(b)

(b) This photomicrograph from another lung with severe radiation pulmonary fibrosis shows the effect of complete lumen obliteration. The dependent respiratory parenchyma, already very fibrotic and relatively avascular, is subjected to further substantial circulatory compromise and is undergoing ischemic degeneration. This change is evident in the right portion of this section.

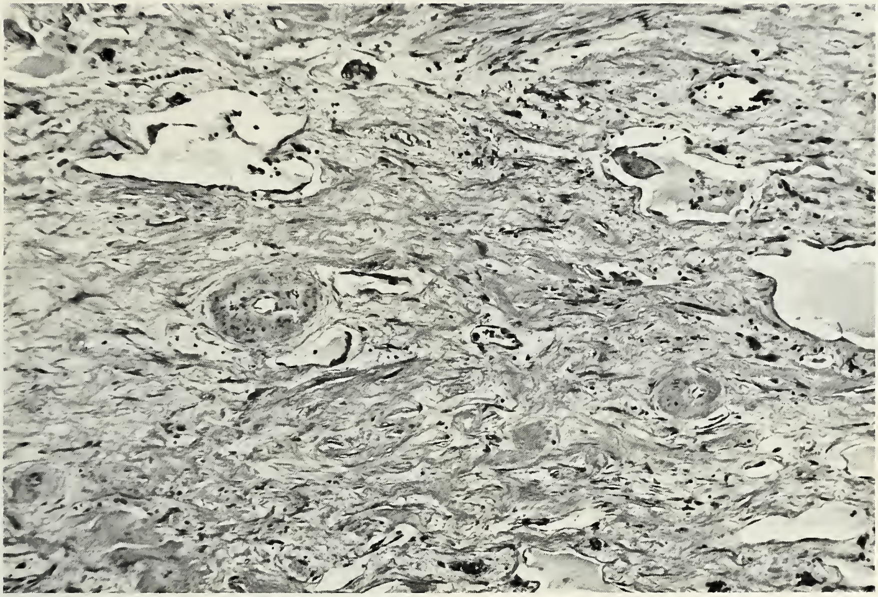
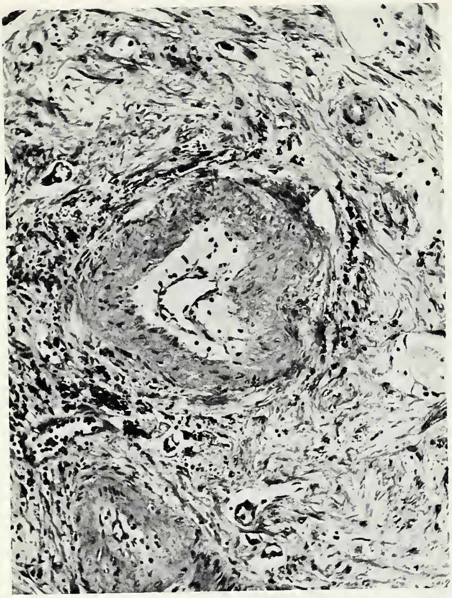


Fig. 4.13 Radiation pulmonary fibrosis. Occasionally, as shown in this photomicrograph, the degree of fibrosis replacement is so severe and so diffuse that any semblance of lung parenchyma is deleted. Only the presence of a few small, widely separated cystic structures lined by flattened, atypical epithelium furnishes evidence of the previous alveolar pattern. Sclerotic vessels are prominent.



(a)

(b)

Fig. 4.14 Late pulmonary vessel changes. **(a)** The progressive constriction of the pulmonary vascular lumens plays an important role in the development of the pulmonary fibrosis. This vessel exhibits subendothelial degeneration with an accumulation of foamy histiocytes. The media is also thickened.

(b) As shown in this photomicrograph, total occlusion of a pulmonary vessel by endothelial proliferation, fibrinoid, or hyaline changes in media or thrombosis may be followed by recanalization.

Chapter 5
Mouth, Pharynx, and Salivary Glands

ORAL CAVITY

Many structural and functional units may be affected by radiation directed at the regions of the oral cavity, oropharynx, nasopharynx, and hypopharynx.

SALIVARY GLANDS

Normal Structure and Function (Three Paired Glands)

PAROTID (SEROUS TYPE). The parotid is the source of digestive enzymes amylase and maltase. It is an encapsulated gland subdivided into lobules by fibrous trabeculae. The secretory tubules are lined with a monolayer of cuboidal serous cells. Under normal circumstances the tubule lumens are not well defined. Long secretory ducts lined with columnar cells that have vertical striations at their bases empty into the excretory ducts whose lining epithelium begins as columnar and becomes stratified squamoid near the outlet. These latter ducts are situated in the trabeculations between the lobules; the smaller secretory ducts are intralobular.

SUBMAXILLARY [MIXED (SEROUS–MUCOUS) GLAND]. The serous alveoli are five times more numerous than the mucous type. The secretory tubules are lined with both mucin-producing and serous cells; however, the distal terminus of the tubule has a cluster of serous cells. The overall structure of the gland is very similar to that of the parotid.

SUBLINGUAL (MULTIFOCAL MIXED GLAND). The numerous small-gland masses consist mainly of mucus-secreting cells. Each has its own excretory duct. The gland composition exhibits a great deal of individual variation.

Clinical Syndrome

Almost invariably incidentally exposed at the time of irradiation of lesions in the oral, pharyngeal, and laryngeal areas. The severity of the acute postirradiation symptomatology relates to the magnitude of the dose and the proportion of the total salivary-gland tissue involved.

WITH LARGE SINGLE DOSES. If all the glandular tissue is affected, there may be rapidly developing dryness of the buccal surfaces due to cessation of secretion. The glands may suddenly enlarge and become painful and tender.

WITH USUAL FRACTIONATION AND MODERATE DOSE LEVELS. There is minimal early effect. The glands are rarely swollen. As the course of irradiation is continued, the saliva seems to lose much of its normal lubricity and becomes more viscous. This appears to be the result of a relative, if not absolute, increase in mucus. Subsequently even this altered secretion may cease with the development of dryness in the mouth and oropharynx. This condition in various degrees of severity may persist for many months and years. The affected gland may become firm and slightly enlarged and may simulate metastatic disease.

Radiation Histopathology

ACUTE RESPONSE (USUALLY SEEN ONLY AFTER LARGE SINGLE DOSE). There is swelling of excretory-duct epithelium (occlusion of lumen) and swelling and rapid degenerative changes in secretory cells (especially serous cells). Interstitial edema is evident as is an inflammatory infiltrate (predominantly granulocytes), probably in response to diffuse cell destruction and perhaps enzyme leakage.

Comment: The basic mechanism of this early acute response is not known. There are at least three possibilities: (1) The direct injury to the nonsecretory, stratified epithelium of the excretory ducts may produce an acute closure of the lumen. This would result in a stasis of the secretions and an acute inflammatory reaction. (2) The secretory cells, and the serous cells in particular, may undergo acute degeneration as a result of direct injury. This would release the cytoplasmic substances into the interstitial tissues and provoke an inflammatory response. (3) The known sensitivity of the endothelium, especially in the microvasculature, may result in a breakdown of the hemic barrier with development of edema and relative tissue ischemia. The glandular cells may respond secondarily to this alteration of their microenvironment.

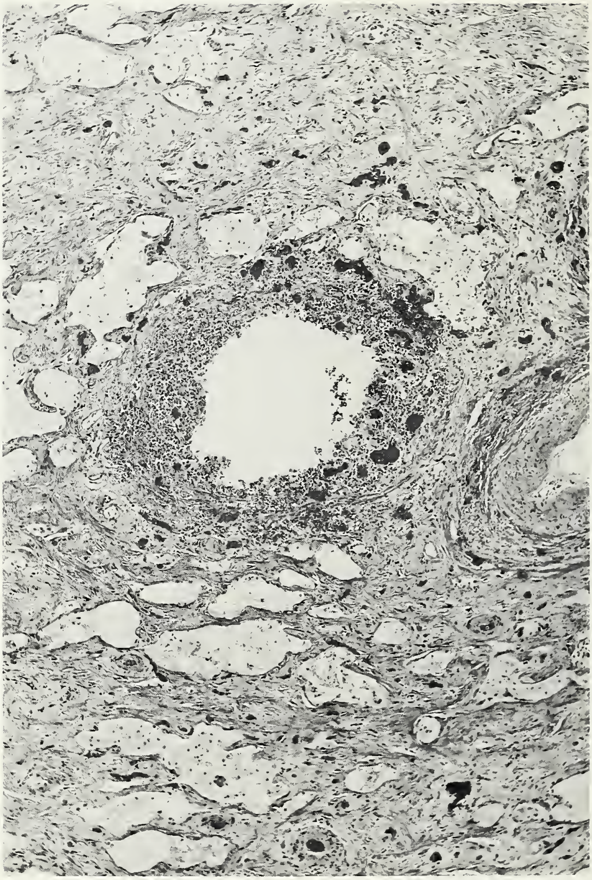


Fig. 4.15 Late complications associated with radiation pulmonary fibrosis. In addition to the potential risk of focal ischemic necrosis, these diffusely fibrosed lungs are susceptible to infections. For example, this photomicrograph shows severe acute necrotizing bronchitis. This infection may be refractive to therapy and prove to be severely debilitating or fatal.

EARLY EFFECTS (AS SEEN WITH FRACTIONATED IRRADIATION). These effects are similar to the effects seen with the large single dose, but they develop over a longer period of time and are of lesser magnitude. There is moderate edema and an inflammatory infiltrate consisting predominantly of lymphocytes and plasma cells with relatively few granulocytes. The epithelial cells undergo a slowly progressive, random degenerative change with a variety of stages observed. The serous cells seem to react earlier and more severely than the mucinous type. Glandular atrophy and interstitial fibrosis are slowly progressive. Where the therapeutic dose is large, the vascular changes, especially in the arterioles and precapillaries, may develop relatively rapidly and amplify the direct injury.

LATE EFFECTS (AS SEEN WITH FRACTIONATED IRRADIATION). There is no defined demarcation between early and late changes. With increasing time postexposure the rate of the progressive early effects diminishes. The processes of random cell degeneration, glandular atrophy, inflammatory cell infiltration, edema, active fibrous proliferation, and duct epithelial metaplasia become relatively static. The late changes are marked by advanced vascular sclerosis with further increasing density of fibrosis, near-to-total atrophy of glandular elements, and relative prominence of isolated nonfunctional ductal structures.

MUCOSA AND CONTIGUOUS STRUCTURES

Normal Structure and Function

The mucosa and contiguous structures are structurally and functionally similar to skin, the major responsibility being that of perpetuating a protective barrier against all forms of injurious agents.

Epithelium

The epithelium is stratified squamous of a moderately active cell-renewal type. The basal or proliferative cell layer is surmounted by nonproliferative differentiating cells. Under normal conditions there is no cornification of the outermost epithelial-cell layers.

Lamina Propria

Supporting the epithelium is a connective-tissue zone containing collagen and elastic fibers (cf. dermis of skin). In some areas papillae project up into the epithelium. Within the stroma is a vascular plexus having numerous radicles that extend to the epithelium. Most areas of the oral mucosa are richly endowed with sensory nerve branches.

Submucosa

The submucosa is present in variable depth in the cheek and soft palate areas but virtually absent in such areas as the hard palate and alveolar ridge.

Comment: The *tongue* is structured basically as above but with some noteworthy differences: (1) It is a mass of interlacing bundles of striated muscle largely encased by mucous membrane. (2) The epithelium of the undersurface is smooth and relatively thin, whereas the superior surface consists of a thickened epithelium of minute papillary composition (three types): filiform, fungiform, and the relatively large circumvallate, which are the loci of the taste buds.

The *tonsillar tissue* in the region of the oropharynx is rich in lymphoid tissue with packed lymphocytes in the lamina propria (often infusing the epithelium itself) and many germinal centers arranged beneath the mucosal surface and under the lining of the crypts, which penetrate deeply into the connective tissue at this point.

Clinical Syndrome

Tumors of the head and neck are frequently effectively controlled by radiation alone or radiation used in conjunction with surgery and/or chemotherapy. Most of these neoplasms, however, are relatively unresponsive to radiation and require total doses in the range of 5000 to 6000 rads.

Considerable response of contiguous normal tissues is expected even as associated with the most cautious application.

ACUTE RESPONSE (DURING THERAPY AND IMMEDIATELY THEREAFTER)

1st week:
Essentially asymptomatic, slight focal hyperemia and edema in more "responsive" individuals.

2nd week:
Increasing soreness of mucosa which makes deglutition difficult and painful. This plus the onset of dryness decreases the desire to eat. Hyperemia (erythema) and edema are very much in evidence.

3rd week:
The mucositis with associated swelling and the marked depletion of gland secretion continues to make the act of mastication and swallowing most difficult. The saliva present is viscid.

4th week:
The changes already present worsen, and there is evidence of irregular areas of mucosal slough.

5th week:
This marks the peak of the clinical response since irradiation is generally halted at this level (5000 to 6000 rads). Maintenance of adequate nutrition and relief of discomfort are of primary concern. The denuded lamina propria is coated with a tenacious pseudomembrane. Resolution of this acute response takes a slow pace, and, during this period of several weeks, good oral hygiene is imperative.

Comment: Occasionally a deeply invasive tumor responds dramatically to the radiation with extensive necrosis. This tissue breakdown may involve major vessels with consequent hemorrhage.

EARLY DELAYED RESPONSE (SEVERAL WEEKS TO SEVERAL MONTHS AFTER COMPLETION OF RADIOTHERAPY). The healing phase of the acute response may have relined the denuded areas. This replenished mucosa is usually thin and somewhat delicate, and underlying telangiectatic vessels are readily visible.

There may be persistent ulceration or the development of a new ulcer spontaneously or as a result of relatively minor trauma. *Comment:* As in the delayed radiation dermatopathies, it is essential that recurrence of tumor be determined before additional definitive therapy is instituted. There is continued dryness in the mouth which makes swallowing uncomfortable. This depletion of saliva production may persist for several months, and recovery is usually limited.

LATE DELAYED RESPONSE (BEYOND 1 YEAR). The condition of the mucosa stabilizes (atrophic and relatively insensitive). The degree of dryness in the mouth is proportional to the recovery of the salivary glands. As in the skin the progressive scarring and vascular compromise lead to a susceptible mucosa. Relatively minor injuries are capable of producing an ulceration that is frequently refractive to treatment.

Radiation Histopathology

EARLY EFFECTS. 1. Degeneration of radiation-responsive cells in basal layer of epithelium.

2. Suppression of cell division with failure to replenish cells lost through attrition leads to denudation of lamina propria.

3. Capillary dilatation (erythema).

4. Swelling of endothelium and smooth-muscle cells in microvasculature-acute relative tissue ischemia and breakdown of hemic barrier [produces edema and extravasation of erythrocytes and granulocytes (mucositis)].

5. Transient hypersecretion of mucous glands followed by suppression of secretion (plugging of ducts by inspissated mucus or swelling of ductal epithelium).

6. Denuded and ulcerated mucosa becomes covered by an adherent pseudomembrane consisting of fibrin and granulocytes.

7. Destruction of large numbers of lymphocytes in the tonsillar areas.

8. With the completion of the intermittent irradiation, the precursor cells of the epithelium are able to initiate cell regeneration.

9. Restitution of the mucosa is often limited with the depth of the regenerated epithelium much less than in the preirradiated state.

10. An epithelial metaplasia may develop in the ducts of the mucous glands, effectively blocking the secretions.

11. There is beginning fibrosis of the lamina propria and the submucosa.

DELAYED EFFECTS. 1. Atrophy of mucosa with increased susceptibility to intercurrent stress (trauma, infection).

2. Glandular hypoplasia and atrophy.

3. Increasing fibrosis of lamina propria.

4. Telangiectasia.

5. Progressive sclerosis of small vessels with increase in relative local tissue ischemia.

6. Atrophy of muscle elements.

LATE COMPLICATIONS. 1. Ulceration and necrosis.

2. Infection that may become deep seated and difficult to control.

3. Debilitation due to interference with normal function of mouth and tongue.

REFERENCES

Andrews, J. R., P. Rubin, and R. W. Swain, 1958, The Dose–Time Relationship in Radiation Therapy: High Dose, Prolonged Time, Large Volume Radiation Therapy; the Limits of Tolerance, *Amer. J. Roentgenol. Radium Ther. Nucl. Med.*, 79: 64-73.

Calcaterra, T. C., F. Stern, and P. H. Ward, 1972, Dilemma of Delayed Radiation Injury of the Larynx, *Ann. Otol., Rhinol., Laryngol.*, 81: 501-507.

Cherry, C. P., and A. Glucksmann, 1959, Injury and Repair Following Irradiation of Salivary Glands in Male Rats, *Brit. J. Radiol.*, 32: 596-608.

Eneroth, C-M, 1971, The Effect of Irradiation in High Doses on Parotid Glands, *Acta Oto., -Laryngol.*, 71: 349-356.

——, C. O. Henrikson, and Per A. Jakobsson, 1972, Effect of Fractionated Radiotherapy on Salivary Gland Function, *Cancer,* 30: 1147-1153.

English, J. A., M. G. Wheatcraft, H. W. Lyon, and C. Miller, 1955, Long-Term Observations of Radiation Changes in Salivary Glands and the General Effect of 1,000 to 1,750 R of X-Ray Radiation Administered to the Head of Dogs, *Oral Surg.*, 8: 87.

Evans, J. C., and L. V. Ackerman, 1954, Irradiated and Obstructed Submaxillary Salivary Glands Simulating Cervical Lymph Node Metastasis, *Radiology,* 62: 550-555.

Friedman, M., and J. F. Daly, 1963, Combined Irradiation and Chemotherapy in the Treatment of Squamous Cell Carcinoma of the Head and Neck, *Amer. J. Roentgenol., Radium Ther. Nucl. Med.*, 90: 246-260.

——, and J. W. Hall, 1950, Radiation-Induced Squamous Metaplasia and Hyperplasia of the Normal Mucous Glands of the Oral Cavity, *Radiology,* 55: 848-851.

Greenspan, J. S., M. R. Melamed, and A. G. E. Pearse, 1964, Early Histochemical Changes in Irradiated Salivary Glands and Lymph Nodes of the Rat, *J. Pathol. Bacteriol.*, 88: 439-453.

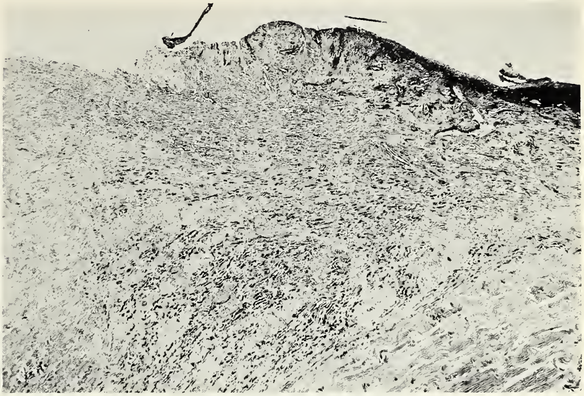
Hudson, W. R., and P. J. Cavanaugh, 1965, Combined Surgical and Radiation Management of Carcinoma of the Laryngopharynx, *Laryngoscope,* 75: 1123-1138.

Kashima, H. K., W. R. Kirkham, and J. R. Andrews, 1965, Postirradiation Sialadenitis: A Study of the Clinical Features, Histopathologic Changes and Serum Enzyme Variations Following Irradiation of Human Salivary Glands, *Amer. J. Roentgenol., Radium Ther. Nucl. Med.*, 94: 271-291.

MacComb, W. S., 1962, Necrosis in Treatment of Intraoral Cancer by Radiation Therapy, *Amer. J. Roentgenol., Radium Ther. Nucl. Med.*, 87: 431-440.

Reed, G. F., 1967, Preoperative Irradiation in Laryngeal Carcinoma, *Arch. Otolaryngol.*, 86: 94-101.

Fig. 5.1 Early ulcerative mucositis. **(a)** This low-power photomicrograph illustrates an early-developing mucosal necrosis with superficial hemorrhage and ulceration. The rather shallow submucosa shows coagulative degeneration and a diffuse inflammatory cell infiltrate. The bands of striated muscle are discontinuous and separated by edematous connective tissue. The muscle fibers are degenerative.



(a)

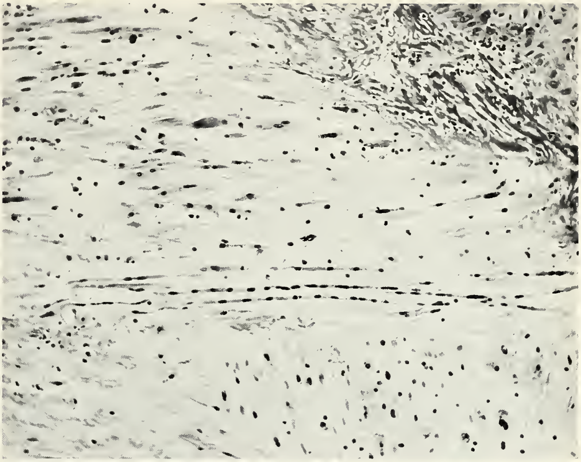
(b) The effect of intense irradiation on the muscle bundles is shown in this high-power photomicrograph. There is loss of muscle-fiber continuity, and the characteristic striated structure of the cytoplasm has been replaced by homogeneity. The muscle-cell nuclei are pleomorphic and hyperchromatic, and clustering of nuclei is frequent. Increased interstitial connective tissue seems to separate individual muscle cells or groups of cells.

(b)

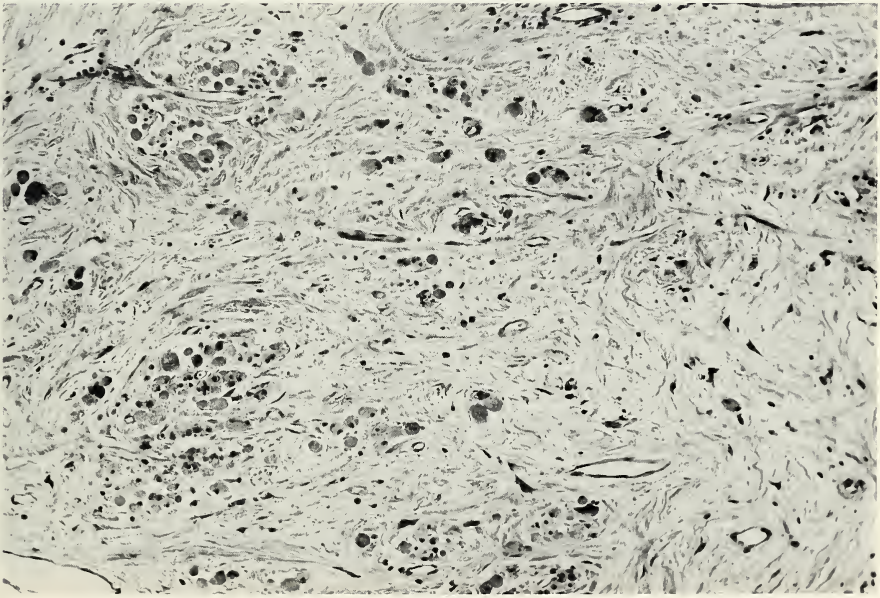
(a)

Fig. 5.2 Early ulcerative mucositis. (a) This photomicrograph shows the edge of an ulcer that is coated with a thick layer of admixed fibrin, necrotic-cell debris, and leukocytes. The base of the ulcer is granulation tissue with superficial coagulation degeneration and increased connective tissue and edema. There is a diffuse inflammatory cell infiltrate. Large "radiation fibroblasts" are scattered throughout the submucosa.

(b) The striated muscle that lies close to the mucosal epithelium frequently absorbs large amounts of radiation and displays relatively rapid progressive degeneration and atrophy. In this high-power photomicrograph, epithelium with underlying coagulation necrosis is evident in the upper right corner. Linear atrophic striated muscle fibers with aligned nuclei are shown in the center of the section flanked by other muscle bundles having dissimilar directional orientation. Note the interstitial edema.

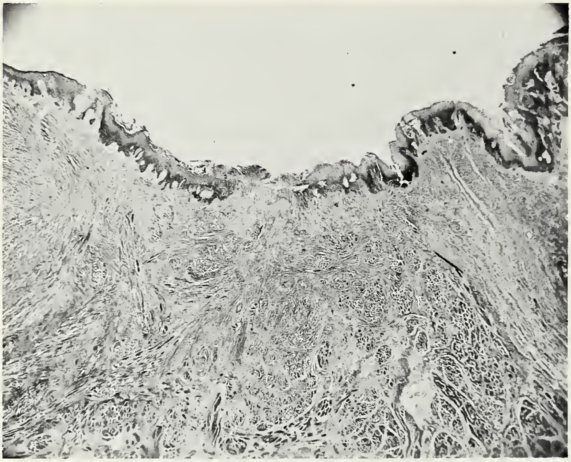


(b)



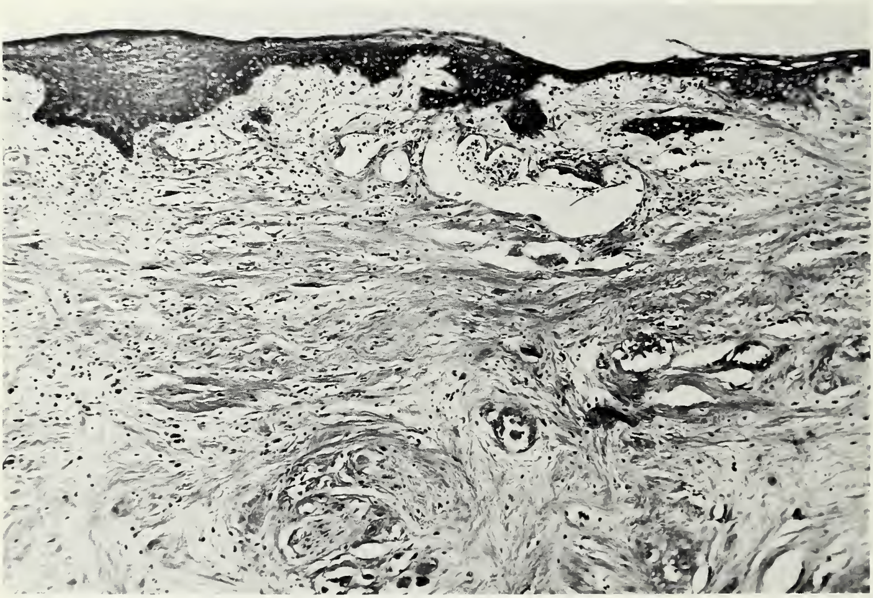
(c)

(c) An end-on or tangential view of these degenerating and atrophic muscle bundles shows muscle fibers of variable size and configuration often separated by edema and increased interstitial connective tissue. The muscle-cell nuclei are hyperchromatic, moderately pleomorphic, and frequently pyknotic.



(a)

Fig. 5.3 Late delayed radiation effect, oropharynx. (a) This low-power photomicrograph discloses a hyperplastic epithelium with focal superficial ulceration on a base of dense fibrous scarring which extends deeply to involve the underlying striated-muscle bundles. There is no appreciable leukocytic infiltration and no hemorrhage.

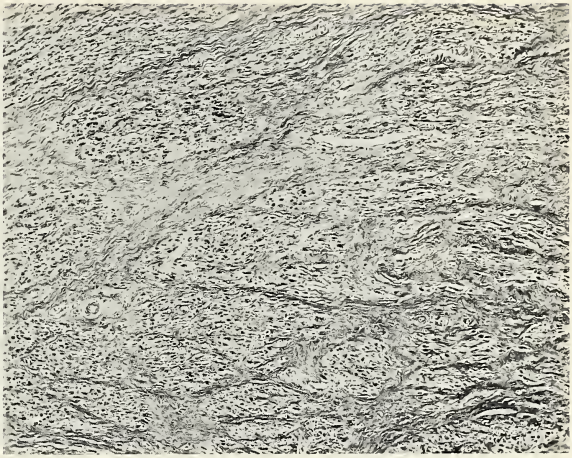


(b)

(b) Elsewhere in the field of irradiation, the appearance at the mucosal surface is one of variable epithelial atrophy, the narrow submucosal zone is edematous with a moderate leukocytic infiltration, and the deeper layers containing residual striated muscle are largely replaced with dense connective tissue. Enlarged and pleomorphic fibroblasts are present.

(c) The deeper tissues consist primarily of muscle bundles and salivary-gland tissue. This low-power photomicrograph is taken through an area of striated-muscle bundles and illustrates the severe fibrosis and muscle atrophy that may pervade the entire field of irradiation.

(c)



(d)

(d) This low-power photomicrograph represents a portion of the submaxillary gland. Most of this mixed gland is of the serous type, which is relatively more responsive to radiation than the mucous variety. A cluster of acini lined with mucin-distended epithelium is shown at the left of this section. The serous acini have been almost totally destroyed with only a few scattered residual epithelial-cell clusters suggestive of the prior glandular pattern. The ducts have been relined by atypical and hyperplastic epithelium of low cuboidal to squamous type. There has been a marked proliferation of the interstitial connective tissue. There is a slight to moderate infiltration of lymphocytes and plasma cells.

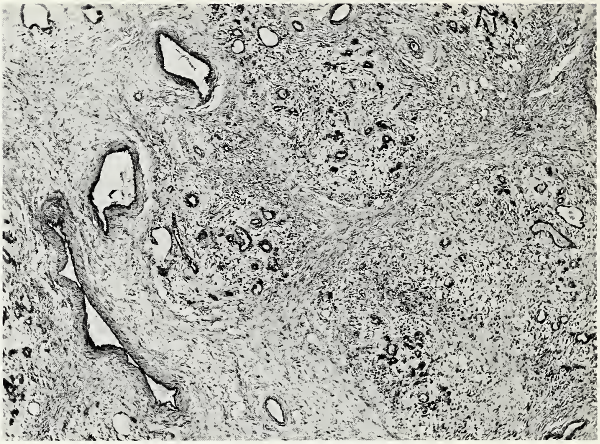


Fig. 5.4 Chronic radiation sialadenitis. (a) The parotid gland frequently lies in the immediate vicinity of the target tissue. This serous gland is responsive to the action of radiation and shows relatively rapid degenerative changes in the epithelium of the acini. Within a matter of months, there may be little or no remaining serous epithelium. The ducts, on the other hand, are prone to show regeneration of the epithelium, which not infrequently is both hyperplastic and metaplastic. The severe fibrosis of the lobules may show also a chronic inflammatory infiltrate.

(b) Other salivary-gland tissues (e.g., the sublingual glands) exist as multifocal structures, each with its own excretory duct system. These clusters of acini with their respective ducts undergo degenerative changes similar to those associated with the larger submaxillary and parotid glands. This low-power photomicrograph depicts such a response to irradiation with the individual fibrosed glands separated by fibrous and adipose tissue.

Chapter 6
Esophagus and Stomach

NORMAL STRUCTURE AND FUNCTION

Esophagus

The primary function of the esophagus is the rapid transport of ingested food and fluid from pharynx to stomach.

The esophagus is a relatively thick-walled muscular tube that consists of an inner mucosa of stratified squamous epithelium several cell layers deep, a submucosa of collagenous and elastic fibers containing scattered small mucous-secreting glands and lymphoid aggregates along with vascular and nerve plexus, and the two outer muscle layers. In the proximal fourth of the esophagus this muscle tissue is predominantly of the striated variety. This type is gradually replaced by smooth muscle, which is present in the distal third of the esophagus.

Although the inner tier of muscle is primarily oriented in a circular fashion and the outer layer mostly longitudinal, there is much interdigitation of obliquely and spirally disposed bundles.

Stomach

The functions of the stomach are threefold: (1) it is a temporary retention facility for recently ingested food; (2) the gastric juices secreted by the epithelium of the mucosa soften and partially digest this food; and (3) the contractions of the thick muscular wall churn this material into a semiliquid chyme, which is subsequently discharged through the pylorus into the duodenum.

In general, the major portion of the mucosa consists of tubular glands, sometimes coiled, often branching, which empty into the bases of the innumerable gastric pits. These pits communicate directly with the mucosal surface.

There are three indistinctly delineated divisions—cardiac, fundic, pyloric—to the gastric mucosa based upon variation in histologic composition and functional characteristics of the glands.

The middle, or fundic, region, which comprises the greatest proportion of the functional mucosa, consists of two major histologic compartments. A mucinogen-secreting tall columnar epithelium uniformly covers the mucosal surface and extends down to the bases of the gastric pits. The gastric glands extending from the gland neck all the way to the muscularis mucosa are lined by four cell types: (1) the zymogenic (chief) cells, (2) the parietal cells, (3) the mucous neck cells, and (4) the argentaffine cells.

The loose matrix of the lamina propria is sparse except for some increase in the neck regions and the areas between adjacent gastric pits. It consists of the microvascular elements within a fine mesh of collagen and reticulin fibers. A few scattered leukocytes may be present.

The muscularis mucosa, lying immediately beneath the gastric glands, consists of two thin layers of smooth-muscle fibers: the inner layer is oriented in a circular fashion and the fibers of the outer layer course longitudinally.

The submucosa is a zone of moderately dense connective tissue traversed by a plexus of major arterial, venous, and lymphatic vessels.

The principal smooth-muscle coats that invest the gastric lining consist of three layers. The inner layer contains fibers running obliquely to the longitudinal axis of the stomach. The thick middle layer is uniformly circular in orientation and is particularly suited to the mixing or churning action. The outer muscle fibers are longitudinally polarized and function principally to propel the stomach contents toward and through the pylorus.

The serosa as in other abdominal viscera consists of a thin zone of loose connective tissue with an outer layer of mesothelial cells.

The rate of cell turnover is not as rapid in the epithelium of the stomach as in the intestinal mucosa; moreover, it has been difficult to ascertain the developmental patterns of the various cell types. Investigations using ^{3}H–TdR (tritiated thymidine) have localized the proliferative activity primarily in the neck region of the gastric glands. It is probable that most of the epithelium, therefore, stems from maturation differentiation of these dividing neck cells.

CLINICAL SYNDROME

Esophagus

EARLY RESPONSE. The early clinical diagnosis of radiation esophagitis is based primarily on symptomatology. Beginning during the *2nd* or *3rd* week subsequent to the initiation of radiation therapy, there may be slight to moderate substernal burning sensation. Occa-

sionally these pains may be sharp and severe and seem to penetrate through to the back. These have been confused with acute cardiopathy. At the same time, there may be the development of dysphagia. Radiographic examination performed at this time will rarely show any significant change.

In most patients who have received standard therapy, this acute esophagitis is transient, and delayed changes of any clinical import would not be anticipated.

Hemorrhage or perforation in this acute phase is rare in an esophagus that was considered normal prior to therapy.

If the treatment has been directed at a neoplasm involving the esophagus, however, the early response is less predictable. Rapid necrosis of a relatively responsive tumor could result in perforation of the esophagus and/or hemorrhage. Occasionally an exuberant desmoplastic tissue reaction is an accompaniment of invading tumor and may become involved in an overall edematous response with early obstruction of the esophageal lumen.

Treatment of the uncomplicated early esophagitis should be conservative and symptomatic. A bland soft diet is advised. If the pain is severe, topical anesthetics may be effective.

DELAYED RESPONSE. The delayed response evolves slowly over a period of several months to years and has as its basis a developing cicatrization and stenosis. Dysphagia may become severe with only liquids passing through the greatly constricted lumen. This complication in its milder form can be satisfactorily treated by mechanical dilatations. Radiographs will assist in the correct diagnosis of this delayed response by showing on barium swallow a characteristic smooth, tapering stricture.

In contrast, delayed radiation effects in the presence of tumor may be most serious with the development of hemorrhage, ulceration and perforation, and fistula formation. Surgery may become necessary to establish some sort of feeding gastrostomy.

Stomach

EARLY RESPONSE. Low level, fractionated doses up to about 2000 R directed at most or all the gastric volume are well tolerated, usually without any significant symptomatology. As cancericidal levels are approached, however, an acute clinical reaction may be expected: (1) anorexia and nausea and (2) epigastric discomfort and vomiting. These effects are usually transient and will rapidly subside following completion of the therapy.

The normal stomach will generally tolerate standard doses with only the preceding evidences of acute radiation gastritis. Contrast-media radiographs are seldom of diagnostic value.

If the therapy is being directed at a very radiosensitive tumor of the stomach wall (e.g., lymphoma), the destruction of the neoplasm may exceed the reparative process, with the development of ulceration with possible hemorrhage and perforation.

Direct visualization of the mucosa by gastroscopy discloses edema, hyperemia, and possible superficial ulcerations consistent with nonspecific acute gastritis.

DELAYED RESPONSE. The onset of symptoms may be relatively abrupt and appear usually several months after the radiotherapy.

Ulcers may develop and will be associated with severe epigastric pain, anorexia, vomiting, and weight loss. In contrast to the peptic ulcer, there is no relationship of this symptomatology to food intake. If the ulcer fails to respond to medical management, surgery is indicated. Radiographs will help confirm the presence of an ulcer but do not establish the etiology.

Dyspepsia is a consequence of chronic atrophic gastritis.

RADIATION HISTOPATHOLOGY

Esophagus

The response must be considered as basically akin to that observed in the skin, oral mucosa, and pharynx because of the similarity of their histologic structure.

EARLY ACUTE (DURING THERAPY AND THE IMMEDIATE POSTTREATMENT PERIOD). 1. Cell degeneration and suppression of mitotic activity in the relatively radiosensitive germinal or basal layer of the epithelium.

2. Loss of intercellular cohesion and bridging—formation of fenestrae—along basal and parabasal layers of epithelium.

3. Microvascular changes including capillary dilatation and defective vascular barrier—edema and extravasation of leukocytes and erythrocytes.

EARLY DELAYED (UP TO SEVERAL WEEKS POSTTREATMENT). 1. Continued cell degeneration without replenishment greatly diminishes the depth of the epithelium.

2. The fenestrae coalesce to form expanding blebs beneath the severely compromised basal layer. This accelerates the slough of the epithelium.

3. If the magnitude of the dose fractions has not been great enough to nullify the reproductive capacity of the precursor or stem cells, focal areas of epithelial regeneration will begin to form along the denuded mucosal surface. This may occur in the early postradiation period even before there has been complete slough of the devitalized residual epithelium.

4. The mucous glands may display variable degenerative changes with subsequent microcyst formation and atrophy.

5. There are developing connective-tissue changes in the submucosa including swelling of the collagen fibers and fibrosis.

LATE EFFECTS (SEVERAL MONTHS TO YEARS). 1. There may be slowly progressive fibrosis in the submucosa even though full restitution of the surface epithelium has occurred.

2. Focal sclerotic vascular changes may become severe with relative ischemia in the dependent tissues. This may in turn further increase the fibrosis and produce variable epithelial atrophy.

3. Telangiectasia may become a prominent feature.

4. As this lesion expands, it may encircle the esophagus with the production of a symptomatic, even debilitative, stenosis of the lumen.

5. This compromised segment of the esophagus is susceptible to additional stress, particularly physical trauma, and may respond by the formation of an ulcer.

Stomach

The mucosa of the stomach, although moderately responsive to radiation, does not react as dramatically as the intestines and is perhaps less sensitive even than the mucosa of the oropharynx and esophagus.

EARLY ACUTE (DURING THERAPY). 1. Suppression of mitoses and degenerative changes in the proliferative cells at the neck region and pits of the gastric glands.

2. Microvascular changes that may be transient—capillary dilatation, interstitial edema, and extravasation of erythrocytes and leukocytes.

EARLY DELAYED (UP TO SEVERAL WEEKS POST-TREATMENT). 1. The loss of lethally injured cells and the lack of cell replacement produce a diminished epithelial-cell population.

2. The relatively unresponsive mature cells appear to remain in situ somewhat beyond their usual biological life-span.

3. Residual cells, some of which may show radiation-induced multinucleation, giantism, and pleomorphism, spread out over the basement membrane in an attempt to compensate for the cell loss.

4. The lumens of deep-lying glands may become occluded by edema of the lamina, cell enlargement, and plugs of accumulated cell debris producing microcysts lined by variably flattened and often distorted epithelium.

5. The preceding effects act jointly to decrease the depth of the mucosa.

6. Although rather difficult to quantitate, there is probably beginning fibrosis of the lamina propria and submucosa.

7. Inadvertent overexposure may markedly amplify the epithelial degenerative effect on the epithelium and a microcirculatory component. The lesion will generally be superficial. Perforation is a possibility.

8. Recovery from moderate early injury may be characterized by focal scarring in areas of acute ulceration, regeneration of gastric glands but often in an atypical pattern, persistent atrophic and sometimes cystic glands, and variable fibrosis of lamina propria and submucosa.

LATE EFFECTS. 1. Evolution of variable chronic atrophic gastritis.

2. Continued slow development of focal vascular injury with the possibility of severe occlusive sclerosis.

3. Progressive fibrosis of submucosa and muscle layers with a concomitant restriction of motility of the gastric wall.

4. Increased susceptibility to stress may result in a refractive gastritis and/or ulceration.

DISCUSSION

The treatment of primary carcinomas of the esophagus and stomach is rather disappointing.

1. These lesions are frequently deeply infiltrating and extensive before they become symptomatic and are discovered.

2. The most commonly encountered carcinomas are not particularly radiosensitive.

3. If significant tumor lysis does occur, there is the very real risk of massive hemorrhage and/or viscus perforation. Fistula formation is not uncommon.

The incidental or unavoidable inclusion of the esophagus or stomach in the field of treatment for a tumor in a contiguous or nearby organ or tissue must always be a consideration in mammary, pulmonary, and mediastinal malignancies; retroperitoneal tumor involvement; and malignancies in the epigastrium other than primary gastric, e.g., lymphoma.

REFERENCES

Bowers, R. F., and I. B. Brick, 1947, Surgery in Radiation Injury of the Stomach, *Surgery,* 22: 20-38.

Brecher, B., E. P. Cronkite, R. A. Conard, and W. W. Smith, 1958, Gastric Lesions in Experimental Animals Following Single Exposure to Ionizing Radiation, *Amer. J. Pathol.,* 34: 105-119.

Engelstad, R. B., 1938, The Effect of Roentgen Rays on the Stomach in Rabbits, *Amer. J. Roentgenol.,* 40: 243-263.

Goldgraber, M. B., C. E. Rubin, W. L. Palmer, R. L. Dobson, and B. W. Massey, 1954, The Early Gastric Response to Irradiation; A Serial Biopsy Study, *Gastroenterology,* **27**: 1-20.

Hamilton, F. E., 1947, Gastric Ulcer Following Radiation, *Arch. Surg. (Chicago),* 55: 394-399.

Hueper, W. C., and J. DeCarvajal-Forero, 1944, The Effects of Repeated Irradiation of the Gastric Region with Small Doses of Roentgen Rays upon the Stomach and Blood of Dogs, *Amer. J. Roentgenol.,* 52: 529-534.

Jennings, F., and A. Arden, 1960, Acute Radiation Effects in the Esophagus, *Arch. Pathol.,* **69**: 407-412.

Roswit, B., S. J. Malsky, and C. B. Reid, 1972, Severe Radiation Injuries of the Stomach, Small Intestine, Colon and Rectum, *Amer. J. Roentgenol., Radium Ther. Nucl. Med.,* **114**: 460-475.

Seaman, W. B., and L. V. Ackerman, 1957, The Effect of Radiation on the Esophagus; A Clinical and Histological Study of the Effects Produced by the Betatron, *Radiology,* 68: 534-541.

Warren, S., and N. B. Friedman, 1942, Pathology and Pathological Diagnosis of Radiation Lesions in the Gastrointestinal Tract, *Amer. J. Pathol.,* 18: 499-514.

Fig. 6.1 Acute radiation esophagitis. This high-power photomicrograph illustrates the similarity between the radiation-induced degenerative changes in the stratified squamous epithelia of esophagus and skin. Damage to the proliferative basal cells reduces cell replacement to a virtual halt. Most of these more sensitive cells undergo degeneration. Those cells which survive the direct radiation insult and the progeny of radiation-altered mitoses become greatly enlarged and pleomorphic. Some areas show abnormal keratin production in the most superficial cell layers. The underlying tissues show minimal effect at this early stage.

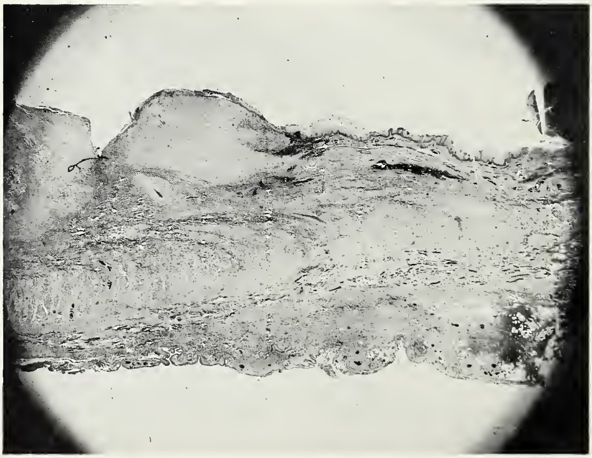


Fig. 6.2 Ulcerative radiation esophagitis. This is a very low-power photomicrograph showing a deep necrotic ulceration at the left edge of the section. Adjacent to the ulcer is a zone of fibrinoid degeneration surmounted by an atrophic epithelium. Note the marked sclerosis of medium and large arteries and associated fibrosis and degeneration in the muscle layer and contiguous external connective tissues.

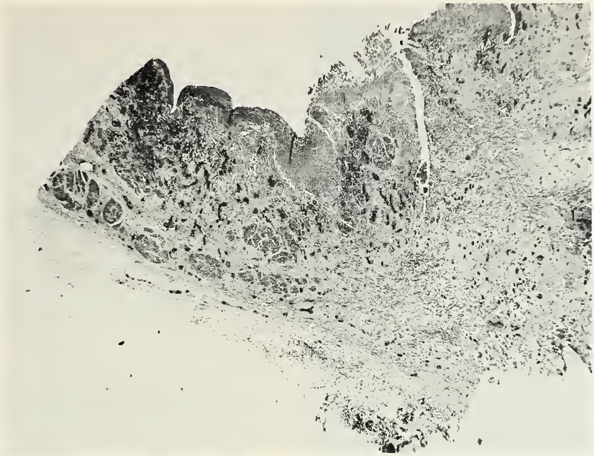


Fig. 6.3 Radiation necrosis of esophageal tumor. One of the problems in the radiation treatment of carcinoma of the esophagus is the frequent inability to correctly assess the extent of tumor involvement. In those cases where there has been covert involvement through the entire esophageal wall, the applied radiation may produce extensive tumor necrosis and promote the development of a fistulous tract communicating with the pleural cavity or contiguous thoracic viscera, especially the tracheobronchial tree. In this section there is full-thickness tumor invasion of the esophageal wall in the right half. The bulk of this carcinoma is necrotic as a result of intensive radiotherapy. The noninvaded wall shows muscle atrophy and fibrosis along with telangiectasia and hemorrhage. Most of the luminal surface is coagulative necrosis with loss of epithelium. At the extreme left edge of this section is a small tag of residual epithelium.

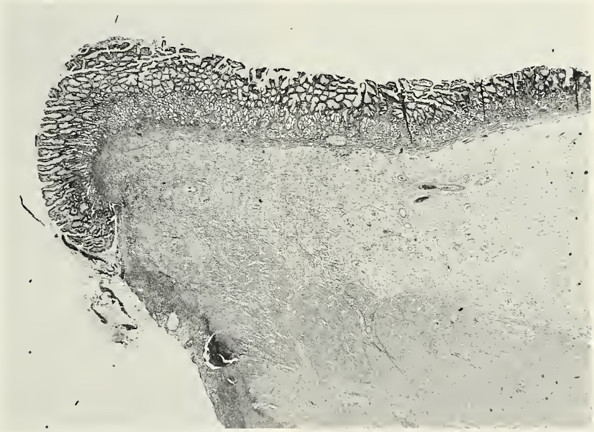


Fig. 6.4 Perforating radiation gastric ulcer. In this low-power view the gastric mucosa is seen to be of near normal depth and structure. The submucosa however is broad and densely fibrotic. The vessels coursing through this zone are markedly sclerotic. The muscle layer is distinct and shows only slight fibrosis. At the left edge there is an abrupt, deeply penetrating ulceration with the base necrotic and coated with fibrin and cell debris.

Fig. 6.5 Radiation gastritis with ulceration. The amount of radiation absorbed seldom exceeds that which would produce an extended period of precursor-cell suppression in the gastric mucosa. In most instances, therefore, the pattern of pits and glands is promptly restored with little or no structural atypism. At the same time, however, the vessels have been injured sufficiently to initiate a slowly progressive vascular sclerosis with associated variable fibrosis of dependent tissue. It is not uncommon to observe essentially normal mucosa lining an area of radiation scarring. The effective supportive reserve of this involved tissue, however, steadily diminishes and increases the likelihood of an ulceration. In this photomicrograph there is some atypia of the glands at the ulcer edge. The submucosa is densely fibrotic and contains vessels with greatly thickened walls and constricted lumens.

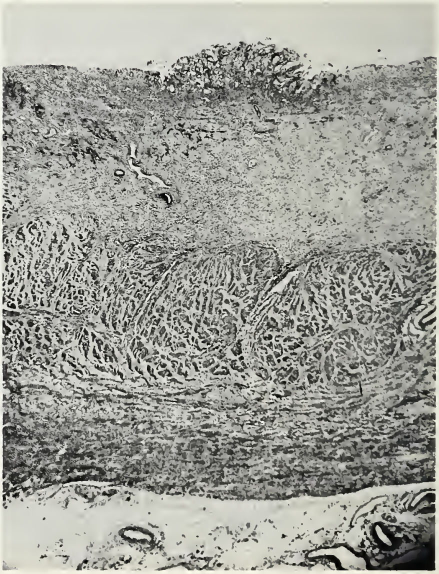


Fig. 6.6 Late radiation gastritis. This very low-power photomicrograph takes in the full thickness of the stomach wall. The mucosa varies from severe atrophy to focal pseudopolypoid glandular hyperplasia. The distinction between mucosa and submucosa is vague with only a few discontinuous strands of smooth muscle to approximate the boundary. The submucosa is broad and fibrotic with the vessels displaying moderate to severe sclerosis. The muscle layers are beginning to show some atrophy with separation of muscle bundles by broadening fibrous trabeculae.

Chapter 7
Intestines

NORMAL FUNCTIONS AND STRUCTURE

Functions

1. The containment and transport of ingested substance (chyme) released from the stomach.

2. The further breakdown and alteration (digestion) of the chyme through the actions of enzymatic secretions of the intestine and its accessory glands.

3. The effective separation of the chyme from the blood and lymph systems by an epithelial barrier that actively absorbs nutritive materials and selectively eliminates certain waste substances.

Structure

The small and large intestines conform in basic structure to the more cephalad segments of the alimentary tract (esophagus and stomach). The intestines are long muscular tubes in linear continuity from the pylorus of the stomach to the anus. The wall is composed of an inner epithelial-lined *mucosa* separated by a thin muscularis mucosa from the underlying *submucosa.* The outer portion of the wall consists of linear, circular, and tangential layers of *smooth muscle.* The bowel is encased in a mesothelial-lined thin serosal membrane except at points of attachment.

MUCOSA 1. In the small intestine the surface area is greatly increased by the presence of *plicae circulares* or thin invaginations of the mucosa which circumscribe the lumen and which remain even when the bowel is distended. These folds are not present in the large intestine.

2. The villi of the small intestine also serve to greatly increase the mucosal surface area. These projections are lacking in the large intestine, whose surface is smooth although pitted by the micro-ostia of the glands of Lieberkühn. The comparable structure in the small intestine are the crypts of Lieberkühn, which open at the bases of the villi. These crypts and glands are the source of the mature functional epithelial cells that cover the mucosa.

3. The epithelium in the small intestine is of simple columnar type and is a rapid cell-renewal system. The focus of cell proliferation is in the crypts where there are three distinct functional compartments:

(a) *Paneth cells (10% of crypt population):* Limited to base of crypt and should be considered separate from the remainder of the cells. These cells appear to have a much slower cell turnover time.

(b) *Proliferative cells (50 to 60%):* Occupy midportion of crypt and are concerned with the production of the principal cells of the mucosa. The generation time is 12 to 15 hr.

(c) *Maturing cells (30 to 40%):* Extend from proliferative zone to the neck of the intestinal gland. These cells are nonproliferative and are undergoing differentiation.

As new cells are formed, they move into the maturation zone and then through the gland neck as fully mature, functional cells. These cells then progress up the villi to eventually be extruded from the villus tip.

The epithelium of the large intestine differs in that there are generally no Paneth cells and the proliferating cells are confined to the basal portion of the crypts but not as sharply demarcated as in the small intestine. The cell turnover time is somewhat longer, although the mechanism of cell replenishment and transit is much the same. There is a greater abundance of goblet cells.

4. The lamina propria of the intestinal mucosa is a loose connective-tissue mesh that separates the crypts and projects into the villi as a central core. In addition to fixed reticulum cells, which appear to be multipotential, there are numerous mobile cells, such as small lymphocytes, plasma cells, and granulocytes, most of which are eosinophiles. Some of these cells penetrate between the surface epithelial cells and enter the gut lumen. Lymphatic tissue in the form of small solitary nodules are numerous, and several may coalesce to form large lymphoid masses (Peyer's patches), especially in the ileum segment of the small intestine.

5. The muscularis mucosa consists of two adjoined very thin smooth-muscle layers (inner circular and outer longitudinal) that are located at the junction of the mucosa and submucosa.

SUBMUCOSA. The submucosa is a relatively dense connective-tissue zone of variable depth. Collagen and elastic fibers are abundant, and scattered aggregates of fat cells are usually present. The submucosa is the site of a rich plexus of blood vessels, lymphatics, and nerves supplying small branches that penetrate the muscularis mucosa and disperse radicles to serve the components of the mucosa.

SMOOTH MUSCLE. There are two major divisions of the smooth-muscle component: The inner layer has been described as having fibers oriented in circular fashion about the bowel and the outer layer is identified as being polarized longitudinally. Medium-sized vessels penetrate these muscle layers from their mesenteric and serosal trunks.

SEROSA. The serosa is a narrow zone of loose connective tissue supporting an external mesothelial membrane.

CLINICAL SYNDROME

Although the small and large intestines are in continuity and of very similar histologic structure, anatomical and functional differences cause variance in the clinical syndromes produced by radiation injury of these divisions.

Both the small and the large intestine are, for practical consideration, equally responsive to the actions of ionizing radiation; however, the incidence of severe injuries is much higher in the large intestine. There are two major reasons for this inequality:

1. Irradiation of pelvic viscera, and, in particular, neoplasms of the uterus, frequently utilizes both the localized intensity of intracavitary radiation sources and external field radiation. The combined dose to the target tissue is high, and, although the isodose falloff is rapid, the rectum and sigmoid segments of the large intestine may absorb hazardous levels.

2. The small intestine is a much more mobile system. Its mesenteric attachments are relatively long, and changes in body position are usually accompanied by a redistribution of the intestinal loops. Even with the body at rest, there is intrinsic bowel motility and slippage. During abdominal irradiation, therefore, segments of the small intestine will receive only a fraction of the total applied dose. Under certain circumstances, however, loops or segments of the small bowel may become relatively fixed in position, thereby offsetting the protection afforded by the inherent mobility. The most common etiologies producing this situation are pelvic inflammatory disease or peritonitis from whatever cause and surgical incursion of the peritoneal cavity. It is appropriate, therefore, to consider the clinical implications of irradiation of the small and large intestines both together and as separate entities.

Early Effects (During Radiotherapy to Several Weeks After Completion)

SMALL INTESTINE. 1. Abrupt onset of intermittent abdominal cramping. By auscultation the bowel is excessively active.

2. There is no significant abdominal-wall muscle spasm or rigidity or tenderness to deep palpation.

3. Diarrhea is usually present, and there may be mild steatorrhea and malabsorption of fat as well as significant electrolyte loss.

4. Contrast-media radiographs would generally be of little value and show only an irritable, hyperactive bowel.

LARGE INTESTINE. 1. Cramping pains in lower abdomen. Bowel sounds may be somewhat hyperactive.

2. The stools are frequent and are usually semiformed. There is associated straining and tenesmus.

3. Proctoscopy will reveal little more than mucosal edema and hyperemia.

Treatment of the early syndromes is symptomatic and supportive. The milder forms are self-limiting and transient, whereas more severe responses may be more or less refractive to conservative management and persist to eventually become ulcerative and/or obstructive.

Delayed Effects (Several Months to Several Years After Irradiation)

The delayed clinical syndrome can be arbitrarily categorized into *early* and *late* components. The former is often an acute and severe exacerbation of an unusually violent and unrelenting reaction developing during or shortly after the radiotherapeutic regime. Occasionally it may develop, as is generally true with the late component, seemingly de novo in irradiated individuals who have displayed only mild or moderate early symptomatology.

EARLY DELAYED EFFECTS

Small Intestine. 1. Rapid development of severe intermittent abdominal pains, nausea, and vomiting.

2. Variable abdominal distention and tenderness to palpation.

3. Decreased bowel sounds.

4. Bowel movements are scanty, occasionally blood tinged, or absent.

5. Muscle rigidity and severe rebound tenderness will be present only if there is peritonitis from an impending or existing perforation.

6. Radiographs of the abdomen will disclose obstruction of the bowel with proximally dilated loops having distinct fluid levels when taken in the upright position.

7. These clinical and radiographic findings are nonspecific insofar as etiology of the obstruction is concerned.

This complication in the small bowel may regress on decompression and supportive therapy. More often than not the acuity of the patient's condition demands laparotomy. Definitive surgery of the affected bowel is unusually hazardous at this stage of radiation injury. The edema and hyperemia may involve large segments of intestine, and the actual point of obstruction may be difficult to identify. Some degree of vascular compromise may exist beyond the apparent demarcation of affected and normal bowel. Failure to adequately resect the damaged loop(s) and to anastamose essentially normal intestine can be disastrous.

Large Intestine. 1. The onset of signs and symptoms is usually several months after the completion of radiation therapy and most often centers in the rectal region.

2. The act of defecation becomes associated with deep-seated pain which encourages voluntary constipation because of the degree of discomfort.

3. The stools are generally reduced in size and blood streaked.

4. If the lesion is located in the sigmoid or higher, there is likely to be an associated diarrhea.

5. If this lesion is present in a female (as is usually the case), manual vaginal examination may localize the painful and indurated tissue.

6. Most such lesions are well within the range of a proctoscopic examination. It is most often encountered on the anterior rectal wall where it is in apposition to the deep posterior vaginal vault because of its frequent etiological relation to the intravaginal radium applicator. Direct visualization discloses an edematous, hyperemic, granular mucosa. Central ulceration may be present, and there are usually small hemorrhagic foci. Because of the poor repair capacity of this irradiated tissue, biopsy should be performed only if the diagnosis is in doubt.

7. When direct observation is not possible, barium enema studies may be of some help. The areas of spasm and mucosal irregularity are consistent with segmental ulcerative colitis and will be of value in assessing the extent of the involvement.

The same radiation-induced tissue compromise that makes surgery of the comparable small intestine lesion hazardous makes it advisable to treat the damaged large intestine and rectum conservatively if at all feasible. Resolution of the edema, inflammation, and superficial ulceration may prove satisfactory with minimal or no residual defecatory problems. Occasionally it may be necessary to perform a bypass procedure to effect acceptable tissue recovery.

Surgical resection and some type of stomal or anastomotic procedure should be reserved for intractable cases, but action should not be delayed to the point of severe patient morbidity.

LATE DELAYED EFFECTS

Small Intestine. 1. Obstructive symptoms may appear many months or years after irradiation and may follow a long latent period of relative well-being.

2. The onset may be protracted and ushered in by vague and intermittent abdominal cramping.

3. More commonly, however, intercurrent inflammation and/or ulceration will instigate greatly accelerated constriction of a bowel segment already fibrosed by radiation and produce severe and colicky pains often associated with nausea and vomiting.

4. There may be proximal bowel distention but not the severe acute tenderness associated with the similar obstructive lesion developing earlier in the postradiation period.

5. Radiographs will be similar to those of the earlier lesion and just as nonspecific. Because the basic pathology is that of dense scarring and vascular sclerosis, there is very little recourse in treatment except that of segmental resection. Although many of these patients are poor surgical risks, it is encouraging to note that in most instances the already extended survival reflects the fact that the treated neoplasm has been controlled or ablated. Recovery from the bowel operation often presages an extended and productive life.

Large Intestine. 1. The only major pathologic feature that differentiates late delayed sequelae from the earlier lesions is the progression of fibrosis in the area of intense irradiation.

2. The sequence of increasing vascular sclerosis and its related dependent tissue atrophy and scarring is amplified by the development of ulcerative lesions and associated inflammation.

3. The stool is frequently ribbon-like or greatly reduced in caliber, and the patient experiences obstipation and very often tenesmus.

4. Direct visualization of the rectal and sigmoidal lesions reveals less acute inflammation than that present in earlier lesions. The mucosa is focally edematous and irregular and discloses superficial vessel ectasia.

5. Because of the scarring, edema, and pain, adequate penetration of the proctoscope may not be possible, and the extent of involvement can be ascertained only by barium enema. The lesions in the colon have a "lead-pipe" appearance, whereas those in the rectum, possibly because of the contiguous scarring, have an "hourglass" configuration. The proximity of most of these lesions to the anal opening makes mechanical dilatation of the stricture one means of conservative therapy along with specific dietary precautions and use of mucosal lubricants.

The development of a rectovaginal fistula alters the outlook from the tolerable inconvenience of stricture to variable incapacitation and profound discomfort. Surgical intervention is frequently necessary.

RADIATION HISTOPATHOLOGY (RADIATION ENTEROPATHIES)

Much of this information relates to the response of the small intestine; however, the effects observed in the colon and rectum are essentially similar.

Early Acute Effects (During Radiotherapy)

The rapid and dramatic mucosal changes associated with single high-dose exposures have been described in detail in the section on whole-body irradiation.

The effects observed during the course of standard radiotherapy are fundamentally similar but take a longer time to evolve and are relatively less devastating because of the repair time allowed by the fractionation of the dose.

In the subsequent description of the changes occurring in the intestines, the sequential events follow a predictable and consistent pattern, although the amplitude of the pathology and pace of progression are to a large degree dose dependent. Assuming "standard" therapy factors, the following early changes can be expected:

1st Week. 1. The overall histologic pattern is not significantly altered.

2. The proportion of crypt cells in mitosis is reduced within 12 hr of the first radiation treatment, and this value continues to decrease throughout this first week.

3. There is a relative increase in cell concentration in the lamina propria.

4. Increasing numbers of crypt cells undergo degenerative changes with consequent progressive diminution of the crypt-cell population.

2nd and 3rd Weeks. 1. There is progressive shortening of the villi with an associated compaction (cellular redistribution) in the basal zone of the lamina propria.

2. The proportion of crypt cells attempting division appears to stabilize at a very depressed level. Mitoses that do form are distinctly atypical with chromosome clumping, lagging, and bridging.

3. If some form of nuclear or total cell division is achieved, the viable daughter cells of these irregular mitoses are frequently morphologically abnormal and are, in all likelihood, incapable of any additional cell division.

4. There is continued loss of epithelial cells by physiological attrition and by radiation-related cell death. The concomitant persistence of mitotic inhibition throughout the radiotherapy precludes the provision of cell replacement.

5. In much the same manner as observed with single high-dose exposures, the bowel acts to compensate for the progressive reduction in mucosal epithelial-cell population by:

(a) Reduction in villus height.
(b) Foreshortening of crypts.
(c) Extended retention time for villus cells and a piling up of senescent cells into a syncytium that caps the blunted villus tips.
(d) Spreading out of atypical residual epithelial cells to cover as much of the underlying membrane surface as possible and maintain the integrity of the epithelial barrier.

6. The Paneth-cell population may show some reduction; however, these cells show minimal morphologic alteration. There may be fewer granules in each cell and greater variability of granule size.

7. Capillaries, precapillaries, and arterioles exhibit variable swelling of the endothelial cells with an associated diminished luminal caliber.

4th Week. 1. In addition to the changes already noted, there is a variable infiltration of plasma cells and, in some cases, eosinophiles and mast cells.

2. As a result of the epithelial degeneration and the compaction of the lamina propria, some damaged crypts will be virtually isolated from the gut lumen and form microcysts.

3. By this time a large proportion of the greatly reduced epithelial-cell population may be characteristically large and pleomorphic with relatively few normal mature villus cells remaining.

4. In general, the standard fractionated regime will not produce ulceration, and, in spite of the severe epithelial damage, the barrier remains largely intact although variable functional decrements are possible.

Early Delayed Effects (Up to Several Weeks After Completion of Therapy)

1. On cessation of therapy there is a surge of mitotic activity which may rebound to levels exceeding the preirradiation state.

2. Epithelial regeneration is rapid, and recovery may be near completion with normal villi in evidence within 2 weeks. It is interesting to note that, although the histopathology has been alarming in its severity, it is remarkable that only a small proportion of treated individuals have significant symptoms.

3. The rebound hyperplasia may resurface the mucosa without difficulty; however, in many cases there may be residual irregularity of the crypts or glands and broad distorted villi.

4. With even higher doses this reversion of the mucosa toward the preirradiation state becomes less and less evident. The crypts are frequently distorted and stunted, and many appear cystic. The villi may be greatly shortened, stubby, and irregularly convoluted along the surface.

5. If the applied dose has been unusually large or if there have been concurrent factors that amplify the radiation response, the perpetuation of epithelial integrity may become much more difficult to preserve. Acute ulcerations accompanied by considerable inflammation with narrowing of the intestinal lumen may develop.

Late Delayed Effects (Months to Years After Irradiation)

Subsequent to the early radiation enteropathy, which manifests itself primarily as epithelial and microvascular injury, there is a period of weeks to months during which some degree of structural mucosal stabilization takes place. The extent of this recovery depends largely on the magnitude of the dose and concurrent factors that may have altered the early tissue-response pattern.

If the dose absorbed was small to moderate and there was no superimposition of early ulceration or infection, the recovery level will eventually approach that of the preirradiation state.

Somewhat higher doses and/or associated mucosal—submucosal ulceration and muscle degeneration will often result in significant deviations from the normal architecture. These patients have undoubtedly endured the discomfort and debilitation of an early clinical syndrome, which may or may not have undergone complete regression.

When the early damage has been unusually severe with ulceration penetrating into or through the muscle coats, an interesting histopathological response develops which at a later date can cause some diagnostic concern. As the ulcerative defect repairs, the regenerating epithelial cells may dip deeply into the cavity even to the serosal tissues and become entrapped anywhere in the bowel wall. Although distorted and often cystic glands within muscle and fibrous tissues might produce some consternation, the associated contiguous scarring and the benign morphology of the epithelial cells should lead to the correct interpretation.

Although the early direct effects of radiation eventually attain a reasonably static configuration, very important events are taking place in the supportive compartment of the intestine. Throughout the posttherapy period there has been the slowly progressive evolution of vascular sclerosis. This hyaline/fibrinoid thickening of the vessel walls is random in distribution along the vessels, and this histopathologic pattern helps to differentiate it from the somewhat more diffuse arteriosclerosis picture.

This circulatory compromise may be initially offset by some collateral channels and neovascularization related to the tissue repair. Often, however, there will be progressive focal ischemia expanding to coalesce and occasionally include the full wall thickness. With this relative ischemia there will be atrophy and scarring and a predilection for an acute degenerative episode either developing spontaneously or as a result of relatively minor physiological stress.

In summary, the structural divisions of the bowel wall (mucosa, submucosa, muscle, and serosa) may react to the direct and indirect effects of radiation with a full spectrum of late changes.

1. The mucosa may be of normal depth and with an essentially unaltered glandular pattern, hyperplastic and pseudopolypoid, distorted with atypical epithelial patterns, or flattened and shallow with no villous or glandular configuration. The muscularis mucosa may be intact, fragmented and discontinuous, or destroyed.

2. The submucosa may be of normal thickness, greatly expanded due to edema and/or increased connective tissue, or narrowed and densely fibrotic. The vasculature may exhibit varying degrees of random arterial sclerosis, phlebosclerosis, and telangiectasis.

3. The muscle coats may be normal or somewhat hypertrophic or may exhibit areas of atrophy and dense scarring. Entrapped mucosal glands are often present in areas adjacent to healed penetrating ulcers.

4. The serosa, which is normally a delicate membrane surmounting a zone of loose vascular connective tissue, may be greatly thickened and fibrotic, especially in the vicinity of the ulcerative lesions. Vessels in this region may be large and sclerosed, and there may be a variable chronic inflammatory infiltrate.

5. All the above relate to the late intrinsic reaction of the bowel to radiation and the manner in which the functional patency may be affected.

Mention should be made of the significance of radiation-related fibrosis and inflammation in the connective tissues that ensheath the rectum. This extrinsic response can add greatly to the narrowing of the lumen and make surgical correction of rectal obstruction hazardous and difficult.

The diversity of these late lesions in irradiated bowel reflects the dependence of the histopathological characteristics on a multitude of interacting factors.

REFERENCES

Aldridge, A. H., 1942, Intestinal Injuries Resulting from Irradiation Treatment of Uterine Carcinoma, *Amer. J. Obstet. Gynecol.*, 44: 833.

Ashbaugh, D. G., and J. C. Owens, 1963, Intestinal Complications Following Irradiation for Gynecologic Cancer, *Arch. Surg.*, 87: 100-107.

Brown, F. A., 1962, Gastrointestinal Complications Associated with Radiation Therapy Characteristic, Confusing, or Compounded, *Amer. J. Dig. Dis.*, 7: 1006-1025.

Dean, R. E., and E. S. Taylor, 1960, Surgical Treatment of Complications Resulting from Irradiation Therapy of Cervical Cancer, *Amer. J. Obstet. Gynecol.*, 79: 34-42.

Hagon, J., and M. Borgers, 1966, Ultrastructural and Cytochemical Studies on Karyolytic Bodies in the Epithelium of the Duodenal Crypts of Whole-Body X-Irradiated Mice, *Lab. Invest.*, 15: 1528-1543.

Halls, J., 1965, Radiation Damage of the Small Intestine, *Clin. Radiol.*, 16: 173-176.

Hampton, J. C., 1966, Effects of Ionizing Radiation on the Fine Structure of Paneth Cells of the Mouse, *Radiat. Res.*, 28: 71-83.

Hiatt, N., et al., 1967, Influence of Intestinal Content on Radiation Lesions of the Small Intestine, *Proc. Soc. Exp. Biol. Med.*, 124: 937-939.

Leblond, C. P., and B. E. Walker, 1956, Renewal of Cell Populations, *Phys. Rev.*, 36: 255-276.

Lesher, S., 1967, Compensatory Reactions in Intestinal Crypt Cells After 300 Roentgens of Cobalt-60 Gamma Irradiation, *Radiat. Res.*, 32: 510-519.

Maas, J. M., 1948, Intestinal Changes Secondary to Irradiation of Pelvic Malignancies, *Amer. J. Obstet. Gynecol.*, 56: 249-259.

Montagna, W., and J. Wilson, 1955, A Cytologic Study of the Intestinal Epithelium of the Mouse After Total Body X-Irradiation, *J. Nat. Cancer Inst.*, 15: 1703-1736.

Perkins, D. E., and H. J. Spjut, 1962, Intestinal Stenosis Following Radiation Therapy: Roentgenologic–Pathologic Study, *Amer. J. Roentgenol., Radium Ther. Nucl. Med.*, 88: 953-966.

Quastler, H., 1963, The Effects of Irradiation on Intestinal Mucosal Cell Population, *Gastroenterology*, 22: 1330-1333.

——, 1956, The Nature of Intestinal Radiation Death, *Radiat. Res.*, 4: 303-320.

——, and J. C. Hampton, 1962, Effects of Ionizing Radiation on the Fine Structure and Function of the Intestinal Epithelium of the Mouse, *Radiat. Res.*, 17: 914-931.

——, and F. G. Sherman, 1959, Cell Population Kinetics in the Intestinal Epithelium of the Mouse, *Exp. Cell Res.*, 17: 420-438.

Requarth, W., and S. Roberts, 1956, Intestinal Injuries Following Irradiation of Pelvic Viscera for Malignancy, *Arch. Surg.*, 73: 682.

Roswit, B., S. J. Malsky, and C. B. Reid, 1972, Radiation Tolerance of the Gastrointestinal Tract, in *Frontiers of Radiation Therapy and Oncology*, J. M. Vaeth (Ed.), S. Karger, Basel.

——, 1972, Severe Radiation Injuries of the Stomach, Small Intestine, Colon and Rectum, *Amer. J. Roentgenol., Radium Ther. Nucl. Med.*, 114: 460-475.

Sullivan, M. F. (Ed.), 1968, *Gastrointestinal Radiation Injury*, Symposium held at Richland, Wash., Sept. 25–28, 1966, Excerpta Medica Foundation.

Sterns, E. E., J. A. Palmer, and F. G. Kergin, 1964, The Surgical Significance of Radiation Injuries to Bowel, *Can. J. Surg.*, 7: 407-413.

Strickland, P., and C. Gregory, 1961, Rectal Dose and Rectal Damage in Intracavitary Treatment of Uterine Cancer, *Acta Radiol.*, 56: 289-295.

Trier, J. S., and T. H. Browning, 1966, Morphologic Response of the Mucosa of Human Small Intestine to X-Ray Exposure, *J. Clin. Invest.*, 45: 194-204.

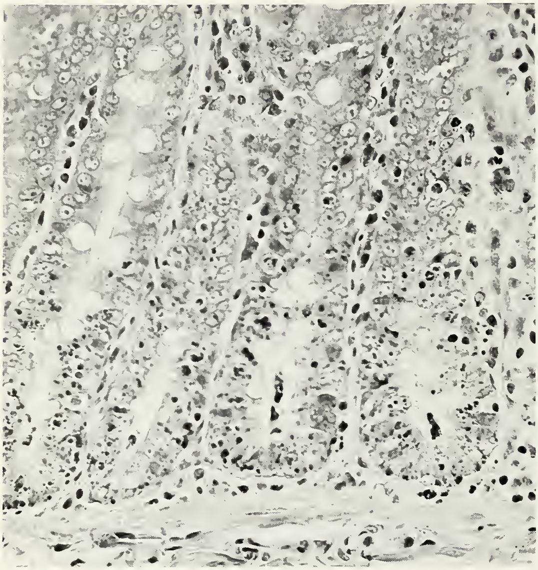
Warren, S., and N. S. Friedman, 1942, Pathology and Pathological Diagnosis of Radiation Lesions in the Gastrointestinal Tract, *Amer. J. Pathol.*, 18: 499-514.

Wiernik, G., 1966, Changes in the Villous Pattern of the Human Jejunum Associated with Heavy Radiation Damage, *Gut*, 7: 149-153.

——, 1966, Radiation Damage and Repair in the Human Jejunal Mucosa, *J. Pathol. Bacteriol.*, 91: 389-393.

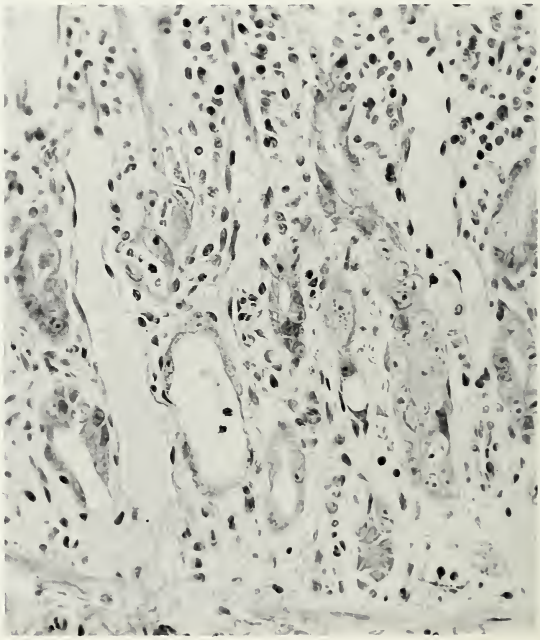
Wiley, H. M., and E. D. Sugarbaker, 1950, Roentgenotherapeutic Changes in the Small Intestine, *Cancer*, 3: 629-640.

Wimber, D. R., and L. F. Lamerton, 1963, Cell Population Studies on the Intestine of Continuously Irradiated Rats, *Radiat. Res.*, 18: 137-146.



(a)

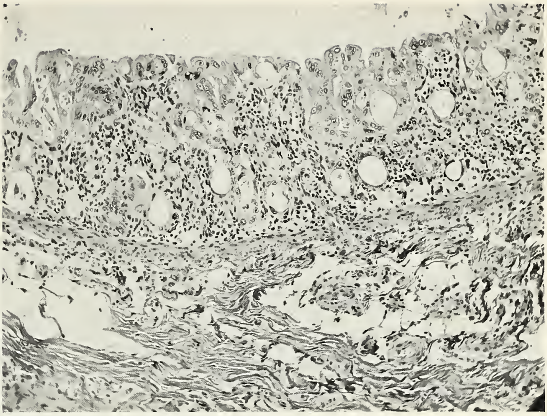
Fig. 7.1 Acute intestinal mucosal response to irradiation. (a) Within a few hours after a single dose of several hundred rads is a period of intense cell destruction in the crypt epithelium which peaks at about 6 hr postirradiation. This photomicrograph of four such crypts shows most of the cells in the proliferative zone exhibiting pyknosis or karyorrhexis. Much of the cell debris appears as irregularly rounded fragments enclosed in small vacuolar structures. Most of this debris is extruded into the crypt lumen.



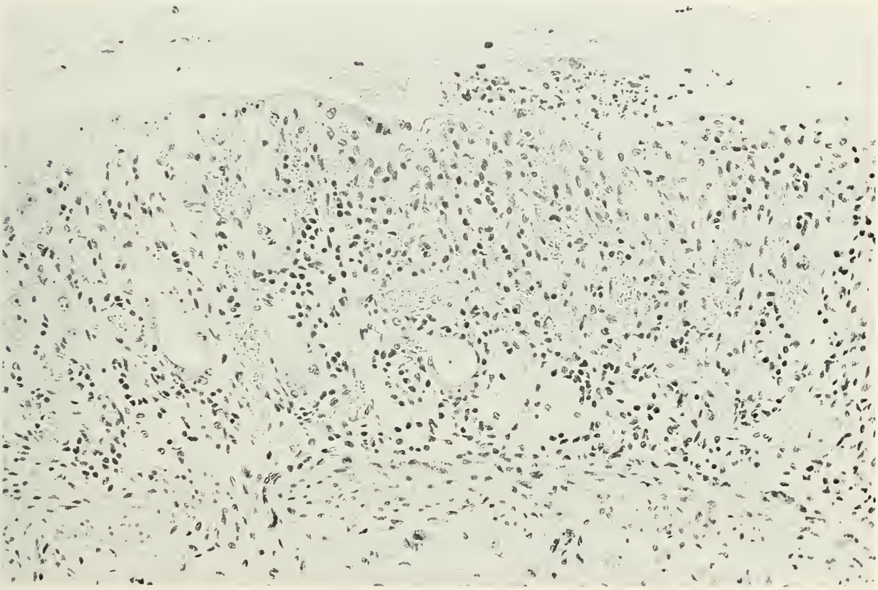
(b) If the regenerative capacity of the crypt epithelium has been severely compromised, there will be a serious delay in the renewal of the lining cells. Failure to replenish the epithelial cells lost as a result of the direct action of the radiation or through usual attrition will dangerously decrease the lining cell population and threaten compromise of this biological barrier. The intestinal mucosa will attempt to compensate for this decrement by shortening the villi and crypts, condensing the core cells of the lamina propria, causing extended retention of the residual epithelial cells, and having these abnormally enlarged cells spread out to cover a maximum surface area of basement membrane. In this high-power photomicrograph of the deep mucosal zone, the thin muscularis mucosa is at the lower edge. The relatively few residual epithelial cells are enlarged and pleomorphic and frequently are attenuated to perpetuate the integrity of the epithelial barrier. Distended lymphatics can be seen between distorted glandular structures.

(b)

(c) After 3 to 4 days with no significant response from the epithelial stem cells, the mucosa has lost most of its villous pattern and is greatly diminished in depth. The bowel luminal surface becomes an almost continuous syncytium of bizarre epithelial cells. In the deeper regions of the mucosa, the residual glands are seen as small irregular cystic structures lined with degenerative and abnormal cells. The lamina propria is a compact mass of connective-tissue elements.



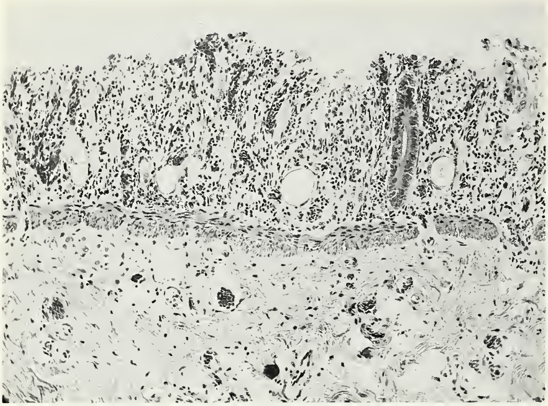
(c)



(d)

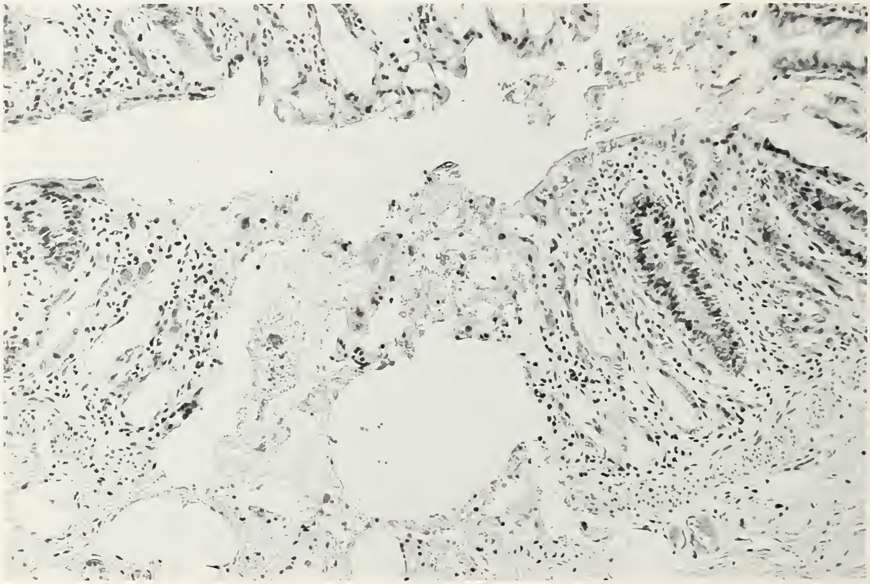
(d) This surface cell syncytium, which is, in effect, a last ditch defense against agents within the bowel lumen, may slough focally to lay bare the thin underlying basement membrane. This break in the epithelial barrier may serve as an entry for toxic or infectious materials and may promote the development of ulceration. Such a focal denudation, coated with an adherent fibrin exudate, is shown in this photomicrograph.

(Figure continues on following page.)



(e)

(e) In 5 to 7 days there is a critical period during which the stem cells may exhibit recovery from radiation injury and begin to repopulate the decimated and collapsed intestinal glands. If the repression of the stem-cell pool has not been excessive, these cells are capable of rapidly reestablishing the continuity of the mucosal epithelium, although the frequency of the glands may be greatly diminished. In this photomicrograph the superficial syncytium has been denuded, a few residual cyst-like glands remain, the micro-vasculature is moderately congested, and there is a single, well-defined, regenerating gland.



(f)

(f) One hazard in this acute period at the time the epithelium is attempting recovery is that the small vessels may become partially occluded as a result of endothelial and smooth muscle swelling. Focal relative ischemia is possible and may produce micro-ulcerations. These superficial lesions may become infected and enlarged. This section shows such an acute microulcer that extends down through the muscularis mucosa. There is minimal leukocytic infiltration at this time.

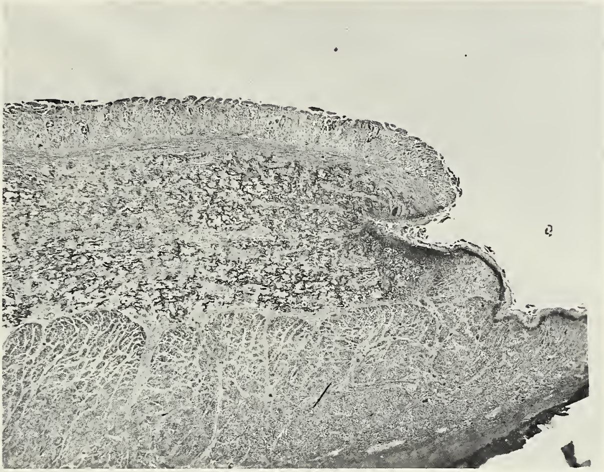


Fig. 7.2 **Early ulcerative radiation enteropathy.** The circumstances of standard radiotherapy seldom produce severe ulcerative intestinal lesions, although less debilitative conditions are not uncommon. This ulcer has developed during a relatively early period, as evidenced by the marked edematous and fibrinoid thickening of the submucosa, the uniform depth of the mucosa with associated residual epithelial abnormality, and the edematous muscle layers. The vasculature lacks the severe focal sclerosis that is typical of the late radiation enteropathies. There is, however, considerable endothelial and smooth muscle swelling and some fibrinoid change that serves to constrict the vessel lumen. This ulcer would appear to reflect the combination of direct radiation injury and secondary circulatory compromise.

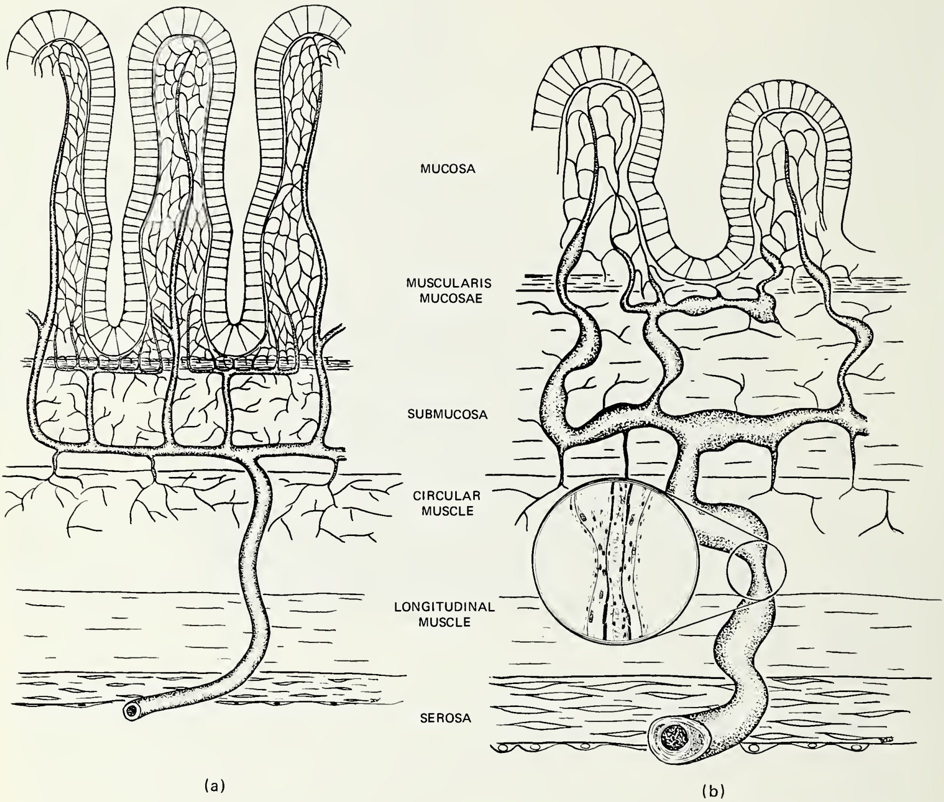


Fig. 7.3 Vascular sclerosis in the late radiation enteropathies. (a) This schematic drawing represents the afferent vascular supply of the intestinal wall. Large branches of the mesenteric artery penetrate the muscle layers giving off many small nutrient vessels along their courses (these vessels are not shown here). Within the submucosa these major vessels subdivide many times to send smaller radicles back into the muscle layer and outward through the muscularis mucosa and into the lamina propria.

(b) In late radiation enteropathy there is a progressive vascular sclerosis that is random both as to site along the vessel and time of development. The inset shows a small segment of artery in greater magnification and demonstrates the variable thickness of vessel wall even within the distance of a few millimeters. The result will usually be irregular foci of tissue atrophy and fibrosis.

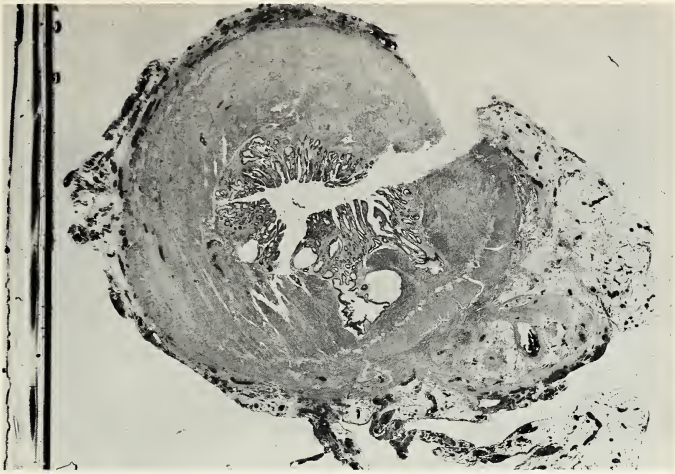
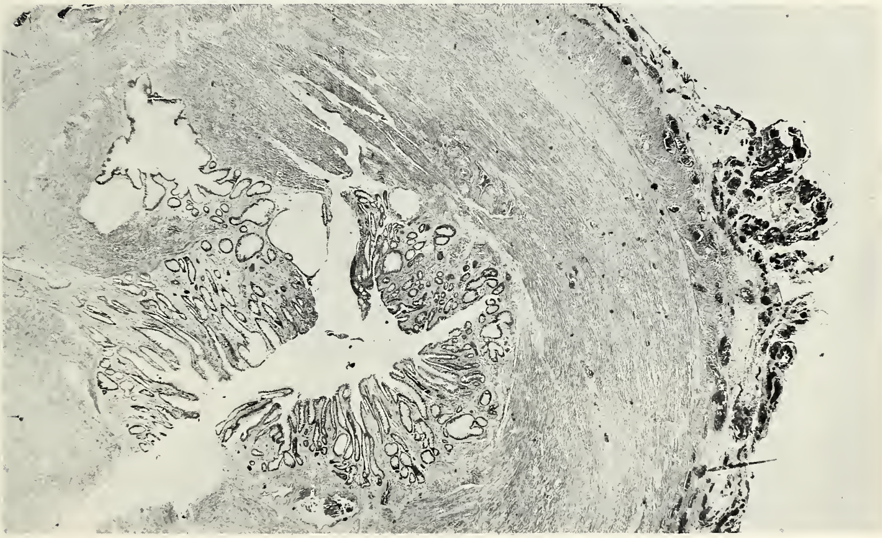
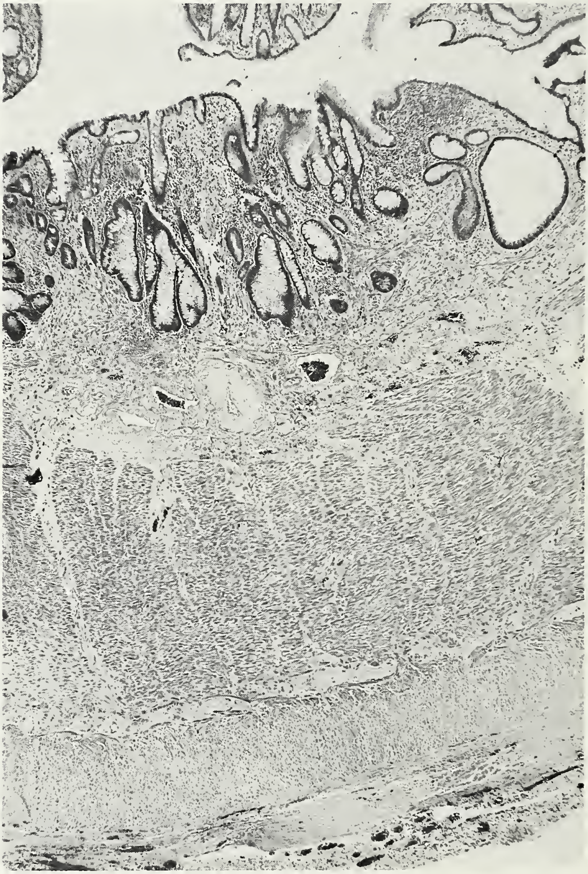


Fig. 7.4 Late delayed radiation enteropathy. (a) This is a very-low-power photomicrograph of a cross section through a radiation stricture of the small intestine. The normal architecture is disturbed by irregular zones of dense fibrosis in the muscle coats, fibrosis of the serosa and mesenteric attachment, a loss of definition of the submucosa, and a greatly distorted and variable mucosa. The bowel lumen has been constricted by these processes.

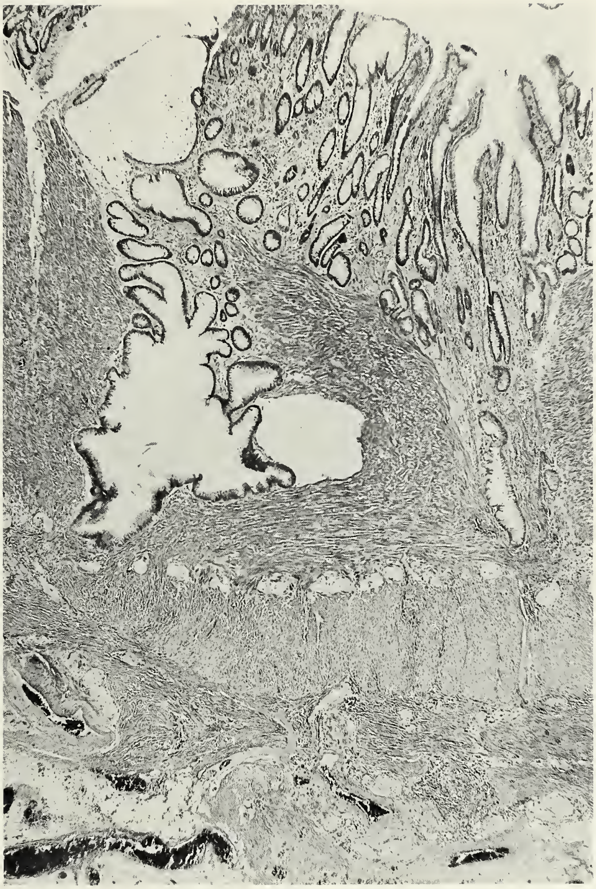


(b) This low-power photomicrograph shows in somewhat greater detail the severe distortion of the mucosal glands. A muscularis mucosa and submucosa cannot be readily identified, and some of the atypical, cystic glands lie deep in the muscle layers almost to the serosa. The vascular pattern has been made more obvious by the irregular sclerosis. Foci of fibrosis are scattered randomly throughout the muscle layers.



(a)

Fig. 7.5 Late delayed radiation enteropathy. (a) This is the same as that depicted in Fig. 7.4. The villous pattern of the mucosa is all but gone in this area. The deep glands are irregularly spaced and of bizarre configuration; some are cystic. There is no clearly defined muscularis mucosa, and the lamina propria and submucosa merge indistinctly. Thick-walled arteries are evident in the submucosal region. There is moderate fibrosis of the outer muscle layer and a focus of fibrosis in the inner muscle.



(b)

(b) This photomicrograph represents an area near that shown in (a) and illustrates the variability of the late radiation response. Some semblance of villi formation is present, although the glands are markedly atypical. There is no defined submucosa, and abnormal glands are shown to lie deep within the muscle and also following along the channels of the penetrating vasculature. Although there is minimal fibrosis in the muscle of this section, there is rather marked vessel sclerosis in the fibrotic serosa. Note that one of the distorted "trapped" glands shows no definite epithelial lining.

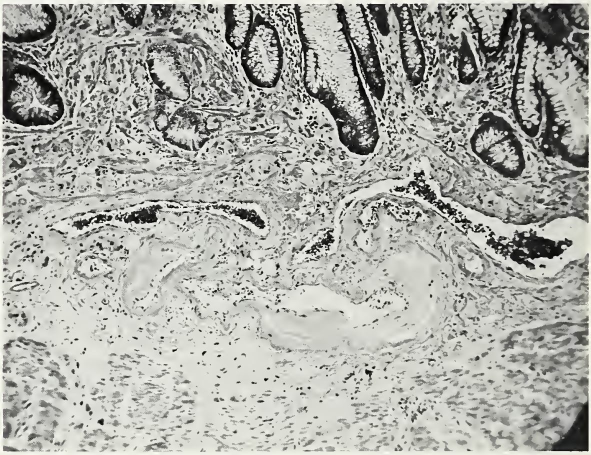


Fig. 7.6 Vascular sclerosis in late radiation enteropathy. This high-power photomicrograph reveals a medium-sized artery cut in near-lineal section. The variable nature of the vessel-wall thickening is clearly demonstrated. The foci of hyaline and fibrinoid accumulation are apparent. The submucosa is narrow and fibrotic and also contains two telangiectatic veins. No muscularis mucosa is identified, although a few discontinuous muscle fibers are present.

Fig. 7.7 Late ulcerative radiation enteropathy. (a) This case is similar to the one depicted in Figs. 7.4 to 7.6 but, in addition, shows a large ulcerative area with apparent perforation through the entire wall thickness at the left. The intense fibrosis of the serosa and attached fat and mesentery are readily identified. Many clusters of atypical glands are shown deep within the muscle.

(b) The submucosa in this area is thicker than normal but is densely fibrotic. In the center is a cavitation deep into the submucosa which has subsequently become resurfaced by mucosa that shows some semblance of the usual villous structure. To the left of this apparently repaired ulcer are many irregular glands throughout the entire thickness of the submucosa.

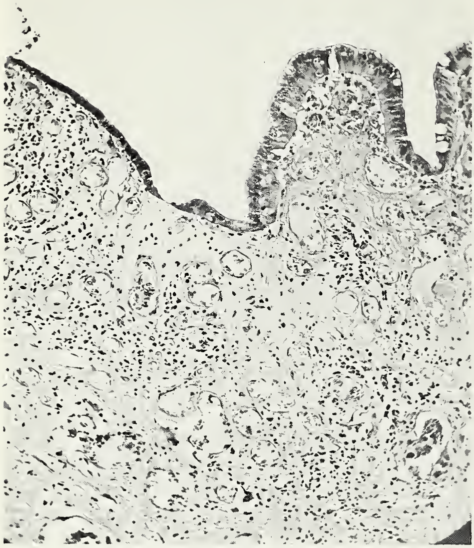
(a)

Fig. 7.8 Late delayed radiation enteropathy. (a) The segmental radiation-induced scarring and bowel-lumen constriction may develop slowly over a period of several years. During this time there may be episodes of acute discomfort related to intermittent partial obstruction and/or ulceration. Usually surgical resection of the involved bowel will be required to restore full patency to the bowel lumen and alleviate the debilitative syndrome. This very-low-power photomicrograph shows such a long-standing constrictive lesion. The lumen caliber has been substantially reduced, and the mucosa is variable but for the most part distorted and atrophic; the submucosa is densely fibrotic with prominent sclerotic and telangiectatic vessels. In most areas the two muscle layers are readily discernable. The serosa and mesenteric attachment are severely fibrosed.

(b)

(b) This photomicrograph is from an area adjacent to the point of stricture and illustrates a deeply penetrating ulceration that has been "filled in" by regenerating atypical mucosa. The disruption of muscle-layer continuity is obvious. There is no clear definition of mucosa and submucosa, and those glands present are markedly distorted and have developed in a rather haphazard fashion.

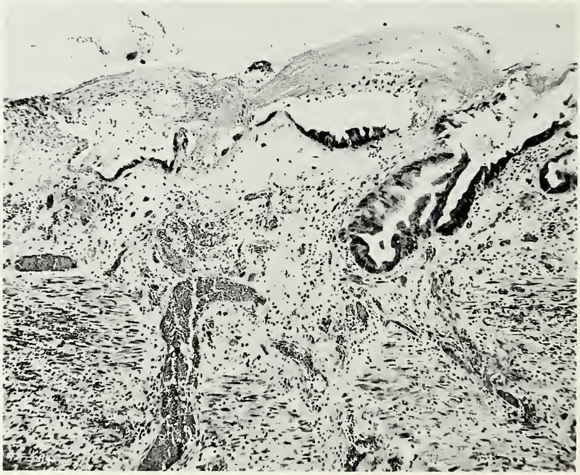
(Figure continues on following page.)



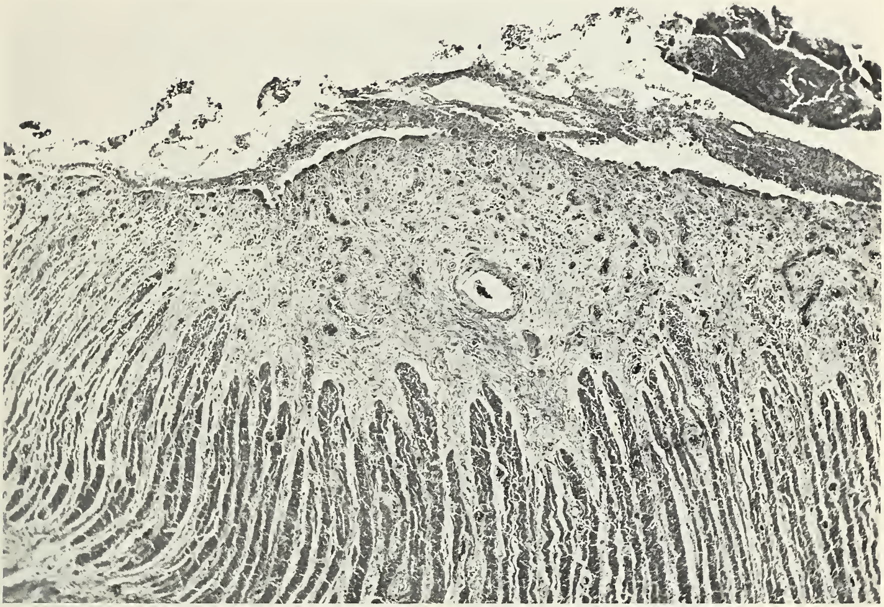
(c)

(c) Some portions of the mucosa have lost all the normal structural characteristics. What rudimentary villi are present are very short and stubby, and the surmounting epithelium ranges from tall columnar to flattened in morphology. The underlying stroma shows no differentiation into mucosa and submucosa, and the muscularis mucosa is absent. Although this subepithelial zone is fibrosed, there are many thin-walled dilated vessels as in granulation tissue. Lymphocytes and plasma cells are present in moderate numbers.

(d) In this photomicrograph the lining epithelium exhibits microfoci of denudation with adherent fibrin tags. Occasionally this atrophic epithelium will dip down into the fibrotic submucosa. There is variable fibrosis in the smooth-muscle layer in the lower portion of this section. The continuity of this muscle appears to be interrupted by penetrating dilated and congested vessels.



(d)



(e)

(e) These microfoci of epithelial denudation may coalesce and result in larger areas of superficial ulceration. These become coated with an adherent exudate but may serve as an entry for pathogens and the development of more deeply penetrating ulcers. This photomicrograph shows the early phase of such a lesion.

(Figure continues on following page.)

(f)

(f) Occasionally these late delayed radiation enteropathies may have the added problem of persistent bleeding. This photomicrograph illustrates the superficial location of a plexus of greatly dilated and congested vascular channels. The overlying dense connective tissue shows a slight chronic inflammatory infiltrate and a few residual distorted glands. The surface is denuded and degenerative. At the bottom of the photograph is a portion of the inner muscle layer of the bowel wall which localizes the severe telangiectasia to the submucosa.

Chapter 8
Liver and Pancreas

Normal Structure and Function

The liver is the largest gland in the body and perhaps the most complex in terms of function. Except for some lipids, all substances absorbed from the digestive tract are transported to the liver. Here, essential materials are metabolized and either stored or disseminated throughout the body. Toxic materials are detoxicated and excreted. The liver also elaborates bile, which is important to the normal digestive process.

The basic structural units are the hepatic lobules. These rounded polygonal units consist of radial cords of hepatic cells extending from the central vein peripherally to the normally indistinct lobule boundary. At the junction of these lobules are the portal triads, which are stellate connective-tissue areas containing branches of the hepatic artery, portal vein, bile duct, and lymphatics.

Separating the hepatic cell cords are the sinusoids. They are interposed between the portal vessels and the central vein and are lined by very flattened endothelial cells. Randomly distributed fixed macrophages (Kupffer cells) appear to be closely associated with this lining. These cells pick up particulate matter and debris as it washes through the sinusoid, and they may be mobilized upon demand.

The flow of blood through the lobule is from the branches of the portal vein and hepatic artery, through the sinusoids, which virtually bathe the hepatic cell cords, and into the central vein.

In a form of counterflow, bile canaliculi arising within the hepatic-cell cords collect the secretions from the cells and conduct this bile to the portal triad areas where the canaliculi empty into branches of the bile duct.

Although this description oversimplifies the very complex liver structure, no purpose would be served in going into greater detail.

Clinical Syndrome

EARLY EFFECTS (TWO TO SIX WEEKS AFTER IRRADIATION). 1. Rapid weight gain and abdominal discomfort. 2. Liver enlarged. 3. Ascites. 4. Abnormal liver chemistries—elevated alkaline phosphatase and serum glutamic oxalic transaminase (SGOT) levels.

Diagnostic aids during this phase include radiogold uptake scan and liver biopsy.

LATE EFFECTS. 1. Functional recovery may be complete or there may be varying degrees of hepatic deficit depending upon the size of the dose and the mass of liver involved.

2. Severe permanent damage may produce recurrent bouts of liver failure with jaundice and ascites.

Radiation Histopathology

The hepatic cells and the epithelial cells lining the bile ducts are conditionally proliferative cell populations. In unstressed circumstances cell division is uncommon; hence the hepatic parenchyma has been considered to be relatively resistant to radiation. An unusual loss of hepatic cells, however, may invoke a wave of increased mitotic activity in the hepatic-cell population and a corresponding proliferation of the bile duct epithelium.

EARLY EFFECTS. Early effects seem to be characterized by nonspecific and inconsistent changes in the centrilobular region primarily referable to possible direct injury to the microvasculature.

1. Dilatation and congestion of central veins.
2. Marked sinusoidal congestion.
3. Variable compression and possible atrophy of hepatic cells in this region.
4. As time postexposure increases, there seems to be a thickening of the vascular walls, especially of the central vein.

DELAYED EFFECTS. Slowly progressive changes seem to be related to vascular sclerosis.

1. Variable cloudy swelling of hepatic cells.
2. Periportal fibrosis.
3. Proliferation of bile ducts.
4. Rapid diffuse necrosis apparently can develop.

PANCREAS

Normal Structure and Function

The pancreas is a large racemose gland having an exocrine component that elaborates digestive juices and an endocrine component that produces insulin.

Present in the exocrine portion are clusters of pyramidal cells contained within a membrane of reticulin fibers.

Interposed between these secreting cells and the alveolar lumens are cuboidal centroacinar cells, which are, in fact, duct lining cells. The intercalated ducts that drain the alveoli combine to form the intralobular excretory ducts lined by cuboidal or low columnar epithelium.

The principal excretory ducts are situated in broad connective-tissue septa and have a columnar epithelium.

Present in the endocrine portion are islets of Langerhans embedded in the exocrine parenchyma. With special histotechnical methods, three types of epithelial cells can be identified (A, 20%; B, 75%; D, 5%). These cells are arranged in irregular cords with a rich interposed plexus of capillaries. Each islet is bound by a delicate mesh of connective-tissue fibers.

Radiation Histopathology

A review of the literature produces only conflicting information with regard to the relative responsiveness of the pancreas and the histopathologic effects. A few general observations are noteworthy, however.

1. Both acinar and islet cells are very resistant (from a morphologic standpoint) to radiation in the range of usual therapeutic procedures.
2. Vacuolation, nuclear pyknosis, and cell degeneration have been identified in the acinar cells after high doses of radiation.
3. There have been isolated reports of pancreatic fibrosis in humans subsequent to the administration of large quantities of radiation.
4. Single acute doses of great magnitude 5000 to 50,000 R produced pyknosis of islet cells.
5. Much additional investigation is necessary.

REFERENCES

Liver

Ariel, I. M., 1951, Effect of Single Massive Doses of Roentgen Radiation upon the Liver: Experimental Study, *Radiology*, 57: 561-575.

Bolliger, A., and K. Inglis, 1933, Experimental Liver Disease Produced by X-Ray Irradiation of the Exposed Organ, *J. Pathol. Bacteriol.*, 36: 19.

Fellows, K. E., G. P. Vawter, and M. Tefft, 1968, Hepatic Effects Following Abdominal Irradiation in Children: Detection by Au-198 Scan and Confirmation by Histological Examination, *Amer. J. Roentgenol., Radium Ther. Nucl. Med.*, 103: 422.

Friedman, N. B., 1942, Effects of Radiation on the Gastrointestinal Tract Including the Salivary Glands, the Liver and the Pancreas, *Arch. Pathol.*, 34: 749-787.

Ingold, J. A., et al., 1965, Radiation Hepatitis, *Amer. J. Roentgenol., Radium Ther. Nucl. Med.*, 93: 200-208.

Kaplan, H. S., and M. A. Bagshaw, 1968, Radiation Hepatitis: Possible Prevention by Combined Isotopic and External Radiation Therapy, *Radiology*, 91: 1214.

Phillips, R., et al., 1954, Roentgen Therapy of Hepatitic Metastases, *Amer. J. Roentgenol., Radium Ther. Nucl. Med.*, 71: 826.

Reed, G. B., and A. J. Cox, Jr., 1966, The Human Liver After Radiation Injury, *Amer. J. Pathol.*, 48: 597.

Samuels, L. D., J. L. Grosfield, and M. Kartha, 1971, Radiation Hepatitis in Children, *J. Pediat.*, 78: 68-73.

Tefft, M., A. Mitus, and N. Jaffe, 1971, Irradiation of the Liver in Children: Acute Effects Enhanced by Concomitant Chemotherapeutic Administration, *Amer. J. Roentgenol., Radium Ther. Nucl. Med.*, 111: 165-173.

——, D. Traggis, and R. M. Filler, 1969, Liver Irradiation in Children: Acute Changes with Transient Leukopenia and Thrombocytopenia, *Amer. J. Roentgenol., Radium Ther. Nucl. Med.*, 106: 750.

Pancreas

Archambeau, J., M. Griem, and P. Harper, 1966, The Effect of 250 KV X-Rays on the Dog Pancreas; Morphological and Functional Changes, *Radiat. Res.*, 28: 243.

Boschetti, A. E., W. C. Moloney, 1966, Observation on Pancreatic Islet Cell and Other Radiation-Induced Tumors in the Rat, *Lab. Invest.*, 15: 565.

Fisher, N. F., J. T. Groot, and A. Bachem, 1926, Effects of X-Rays on Pancreas, *Amer. J. Physiol.*, 76: 299.

Leven, N. L., 1933, Effect of Radiation Emanation on Pancreas of Dogs, *Amer. J. Cancer*, 18: 899.

Rauch, R. F., and K. W. Stenstrom, 1952, Effects of X-Ray Radiation on Pancreatic Function in Dogs, *Gastroenterology*, 20: 595.

Rosen, V. J., and L. J. Cole, 1971, Radiation Carcinogenesis, in *Pathology of Irradiation*, pp. 120-145, C. C. Berdjis (Ed.), Williams & Wilkins Company, Baltimore, Md.

Sommers, S. C., 1971, Effects of Irradiation on Endocrine Glands, in *Pathology of Irradiation*, pp. 408-446, C. C. Berdjis (Ed.), Williams & Wilkins Company, Baltimore, Md.

Volk, V. W., K. F. Wellmann, and A. Lewitan, 1966, The Effect of Irradiation on the Fine Structure and Enzymes of the Dog Pancreas, *Amer. J. Pathol.*, 48: 721.

Warren, S., R. G. Carlstein, J. Steinke, and R. N. Chute, 1964, Island-Cell Tumors in Irradiated Rats in Parabiosis, *Proc. Soc. Exp. Biol. Med.*, 115: 910.

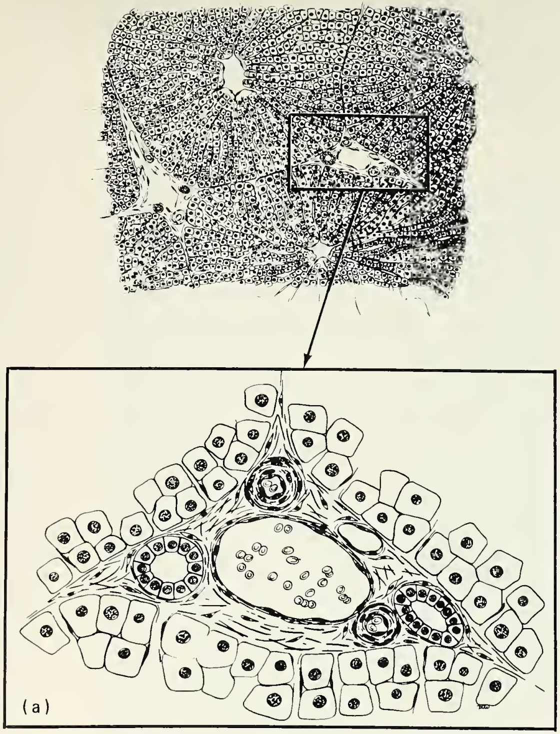
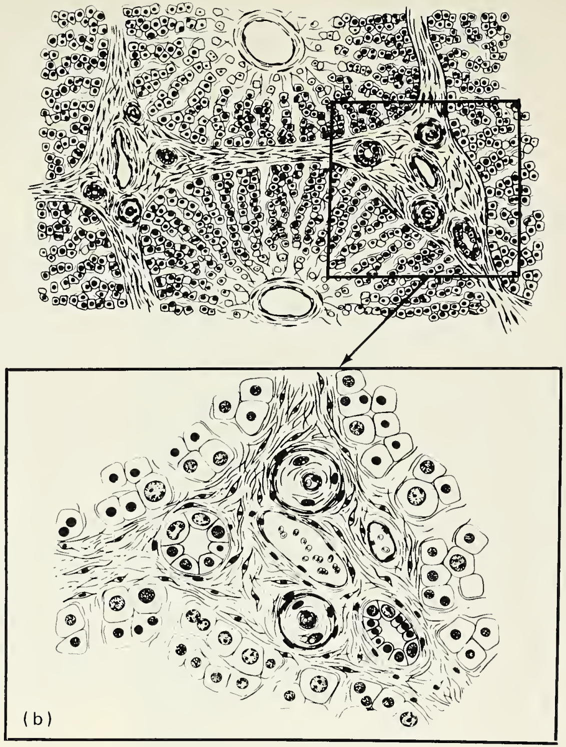
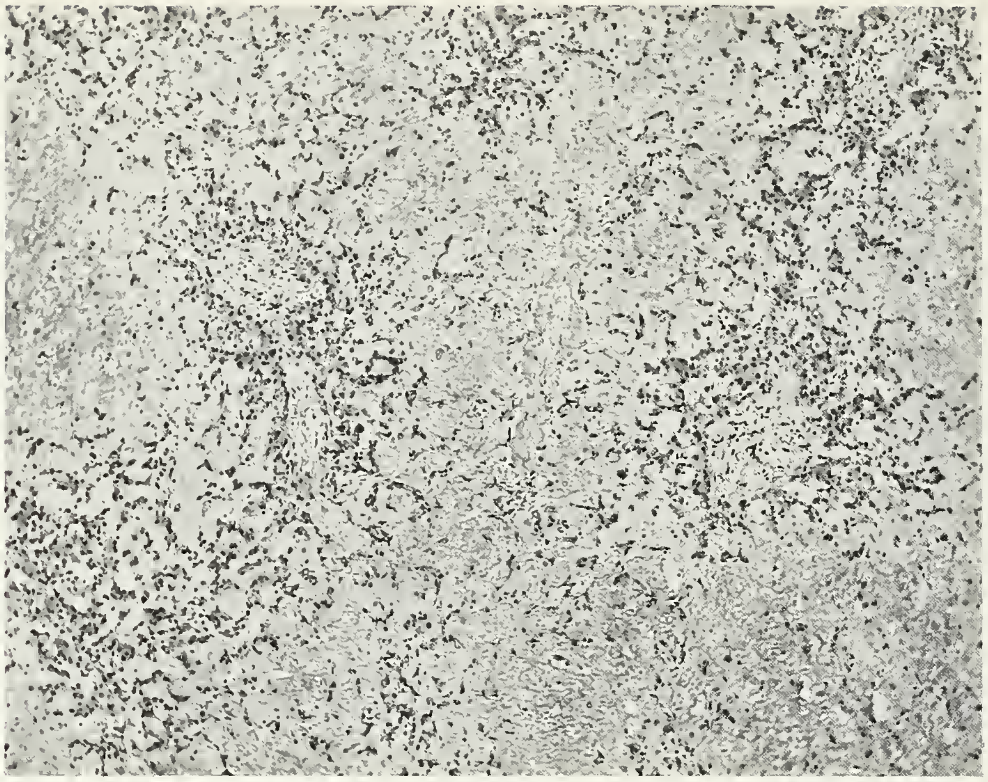


Fig. 8.1 Histology of the liver. (a) The top schematic drawing represents portions of several hepatic lobules with their radial cords of hepatic cells extending from the central veins out to the thin connective-tissue trabeculae that enclose the lobules. The liver-cell cords are separated by sinusoids lined by very flattened endothelial cells and the closely associated phagocytic Kupffer cells. The inset illustrates the components of the portal areas at the juncture of the lobules. These irregularly stellate foci of connective tissue contain branches of the hepatic artery, portal vein, bile duct, and lymphatics.

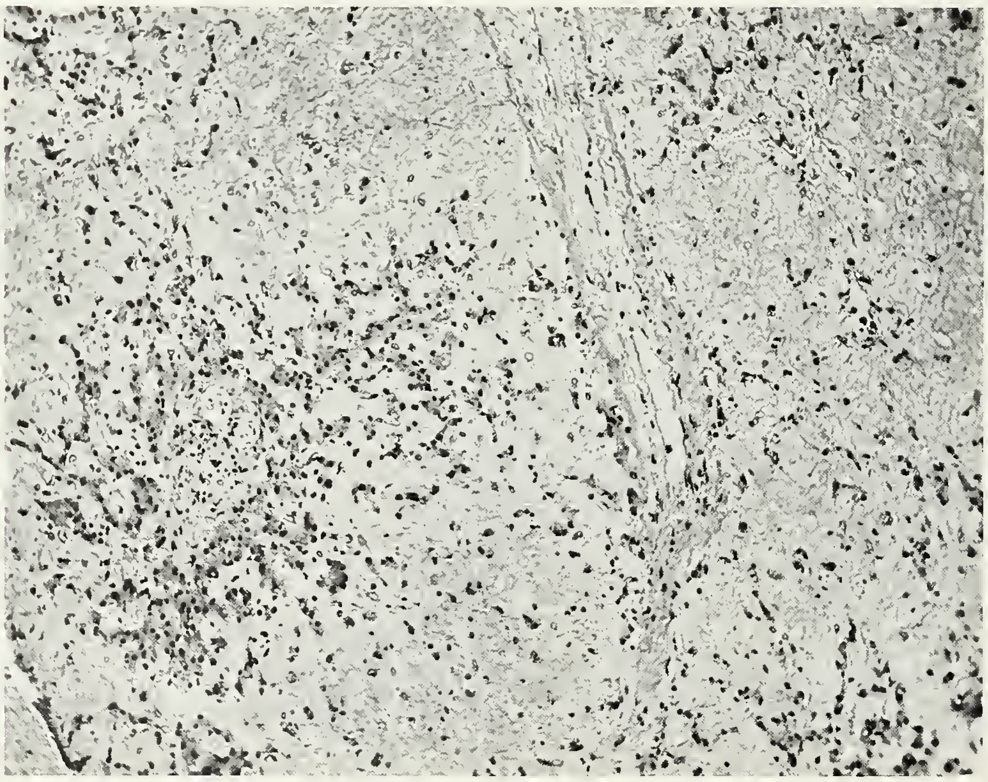


(b) Late radiation changes are depicted in this comparable schematic drawing. The liver lobules are separated by broad bands of connective tissue. The central veins are prominent and exhibit perivascular fibrosis. There is variable atrophy of the hepatic cells in the centrilobular region, whereas those nearer the periphery show moderate nuclear pleomorphism and binucleation. These latter changes are associated with regenerative efforts. The portal areas are greatly enlarged by the increase in connective tissue. The small arteries may show thickening of their walls. Some of the epithelial cells of the bile ducts are pleomorphic.



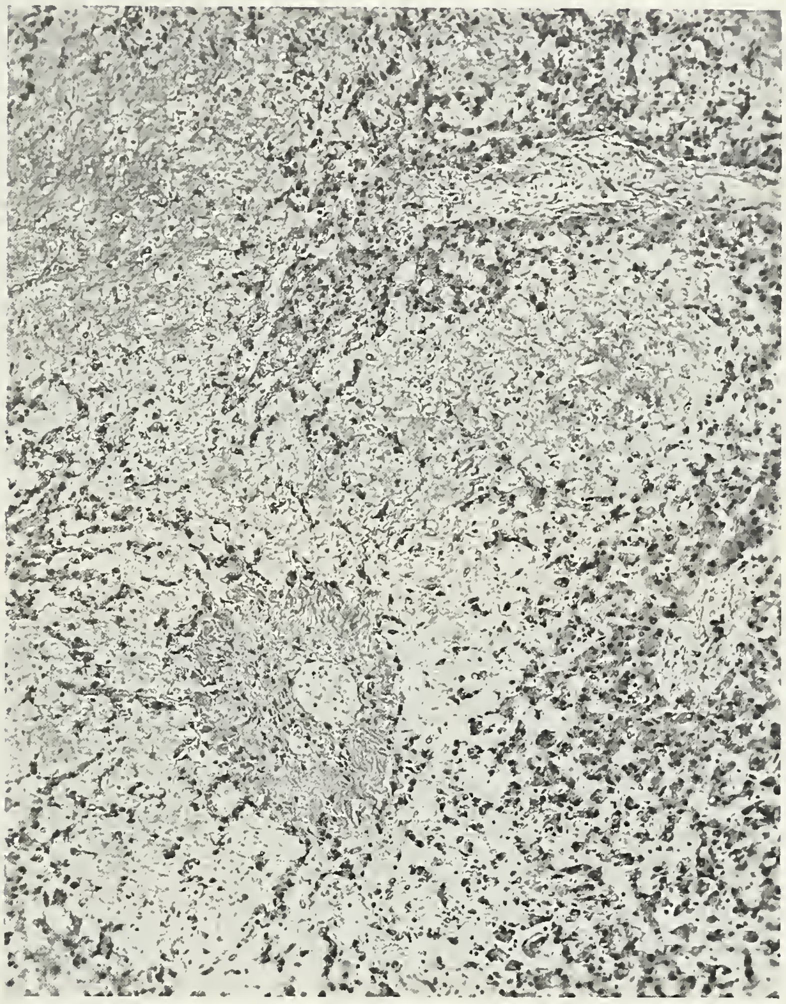
(a)

Fig. 8.2 Delayed radiation effects in the liver. (a) This low-power photomicrograph shows a marked loss of hepatic cells. The degeneration and atrophy of these cells is mainly in the central two-thirds of the liver lobules. At the periphery, especially adjacent to the portal regions, are irregular cords and isolated clusters of hepatic cells. The portal areas display a moderate increase of connective tissue.



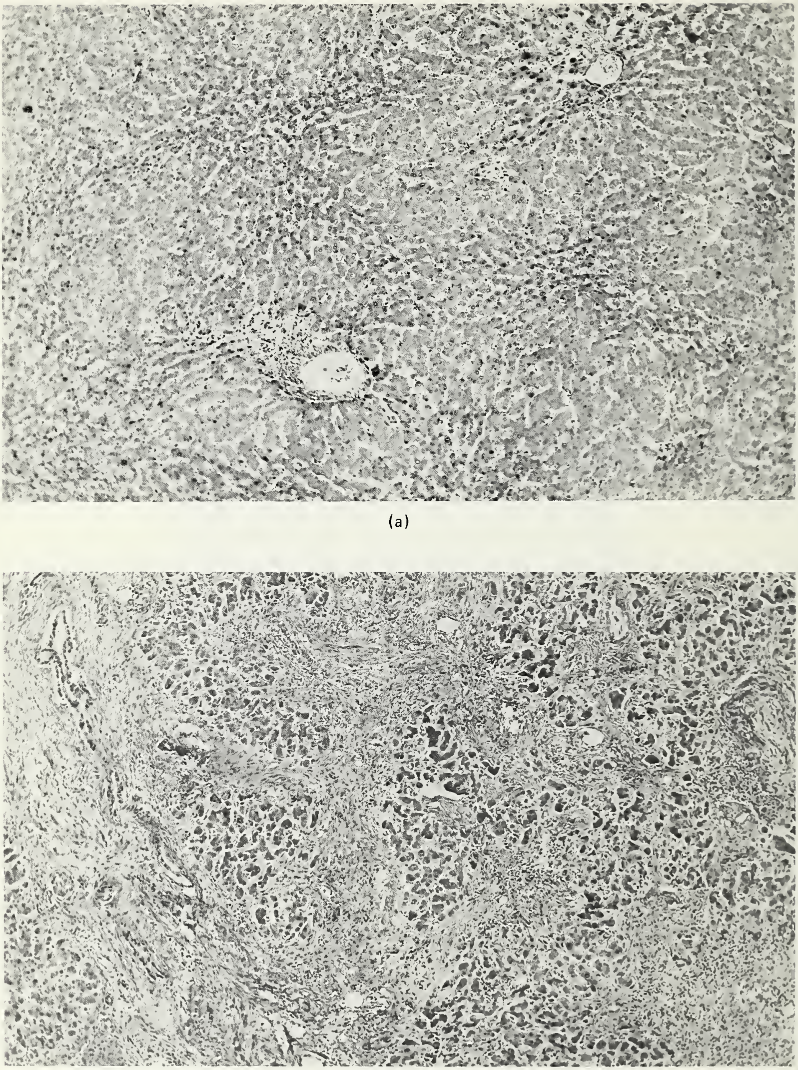
(b)

(b) This higher power view of the liver parenchyma shows a linear section through a central vein. The lumen is relatively narrow with a proliferation of loose subendothelial connective tissue. In addition, this vessel has a perivascular zone of dense collagenous connective tissue. A major portion of the lobule consists of collapsed sinusoids and atrophic hepatic cells in an abundant fibrillary matrix. Remaining viable hepatic cells are moderately pleomorphic; many exhibit binucleation.



(c)

(c) This section shows a branch of the hepatic vein encased in a broad perivascular zone of dense connective tissue. In contrast, the nearby portal area has less prominent fibrous proliferation.

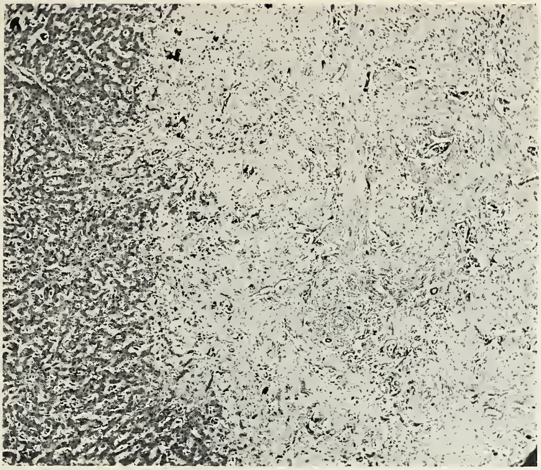


(a)

(b)

Fig. 8.3 Late hepatic radiation fibrosis. (a) The right lobe of this liver was not included in the radiation field. This low-power view discloses essentially normal liver parenchyma.

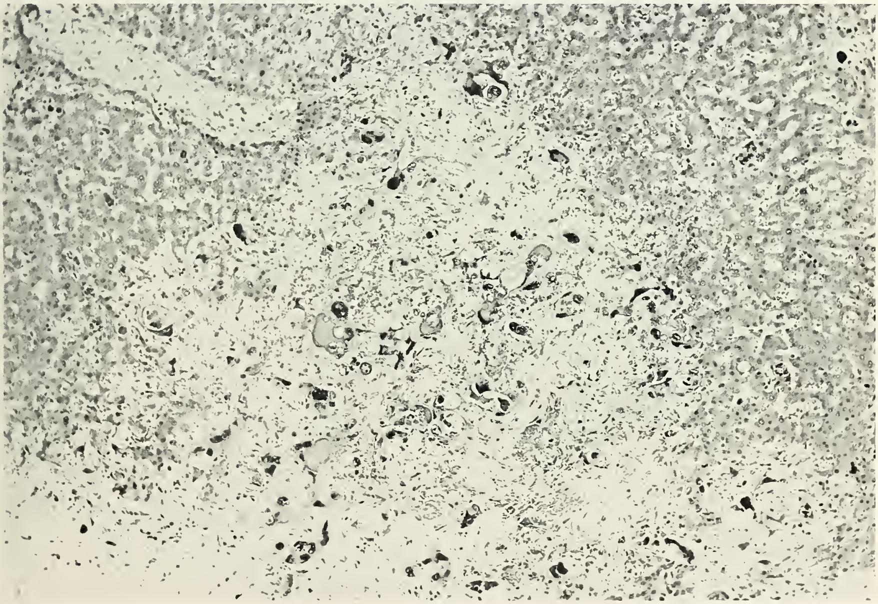
(b) During the treatment of a lymphoma of the epigastric region, the left lobe of the liver received a large amount of radiation. At autopsy, several months later, this lobe was noted to be small and nodular. The lobular structure is seen to be markedly distorted by broad bands of fibrous tissue that incorporate the portal regions. There is variable fibrosis about the central veins as well.



(a)

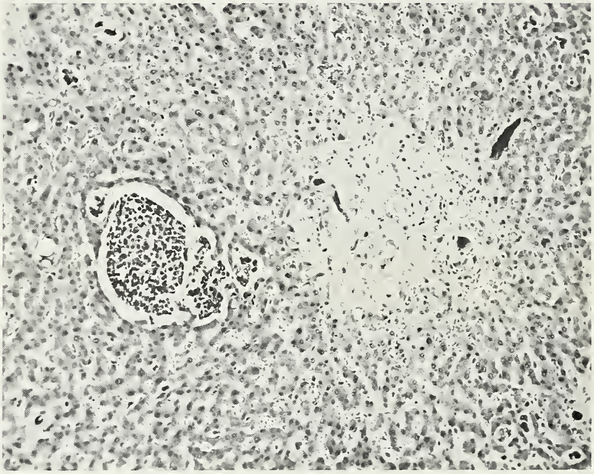
Fig. 8.4 Irradiation of metastases in the liver. **(a)** Although there is seldom any lasting benefit in the irradiation of liver metastases, it is not uncommon to observe some degree of tumor lysis with aggressive palliative irradiation. Most lymphomas, for example, respond well to this treatment. This low-power field shows a large metastasis from an undifferentiated lung carcinoma that received palliative radiotherapy. The near total ablation of tumor cells reflects the efficacy of the treatment.

(b) There are residual tumor cells present in some of the treated nodules. These cells however are greatly enlarged and severely distorted as a result of the irradiation. None show any evidence of mitotic activity, and it is reasonable to assume that no proliferative cells are present (effective cell "death").



(b)

(Figure continues on the following page.)



(c)

(c) The ultimate futility of this therapy is indicated in this photomicrograph. A small nodule of tumor has been "sterilized" by the irradiation. A few cell cords away is an irregular mass of proliferating undifferentiated cells apparently representing a metastasis that has occurred subsequent to the radiotherapy.

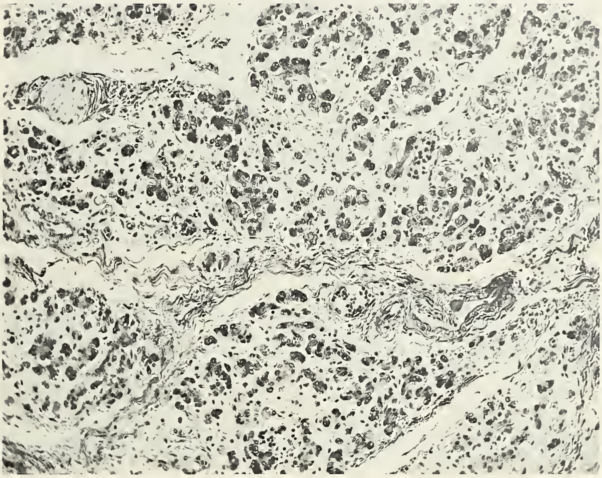


Fig. 8.5 Delayed radiation effect in the pancreas. Several months prior to death, this individual had received intensive radiotherapy to the para-aortic lymph nodes for the control of testicular embryonal carcinoma. Although the pancreas is relatively unresponsive to radiation, large doses may have some direct cellular effect and will certainly produce vascular sclerosis. In this photomicrograph the vessel changes are not impressive; however, variable acinar cell degeneration and an increase of interstitial connective tissue are present. Islet cells (not seen in this section) were not significantly affected morphologically.

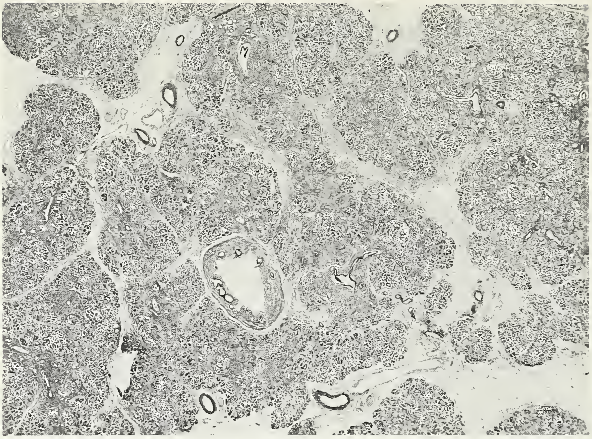
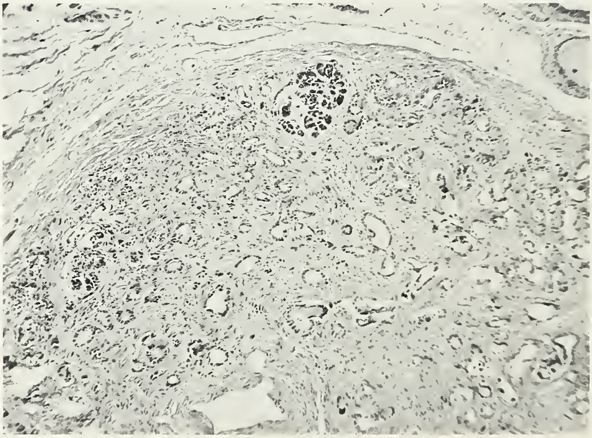


Fig. 8.6 Late radiation changes in the pancreas. (a) This low-power photomicrograph represents changes observed in the pancreas of an individual who, several years earlier, had received a large dose of radiation in the upper abdominal lymph nodes for Hodgkin's disease. Although the parenchymal pattern is unaltered except for some broadening of the fibrous trabeculae, large, irregular foci of lobule fibrosis are found throughout this section.



(b) This high-power photomicrograph illustrates one of the areas of parenchymal fibrosis. Most of the acini are gone, but the residual ductal structures are relatively prominent. The islands of Langerhans appear relatively well preserved.

Chapter 9
Kidney

NORMAL STRUCTURE AND FUNCTION

The kidneys are paired mirror-image organs that eliminate water and at the same time selectively excrete specific waste substances present in the blood. These processes, however, are regulated by complex demand–release mechanisms such that only those amounts in excess of the requirements for stabilized metabolism are eliminated.

The glomerulus provides a highly efficient filtration system inserted into the blood circulation of the body. Although the amount of filtrate thus formed is very small in comparison to the volume of blood forced through the glomerular capillary bed, it is even further reduced and concentrated by active reabsorption in the tubules; i.e., 1300 ml of blood per minute courses through the kidneys with the glomeruli extracting only 125 ml of filtrate from this volume. The tubules then reabsorb most of this, and only about 1 ml of the initial quantity passes through the collecting tubules.

The tubules by both active and passive reabsorption and in some instances excretion enforce further the regulatory demands that maintain the composition of the fluid environment of the body at levels compatible with normal physiological function.

Gross Anatomy

The kidneys are situated paravertebrally in the loose, areolar connective tissues of the retroperitoneal space. The upper poles are usually at the level of the 12*th* thoracic vertebra. The outer mass of the kidney is the cortex. This well-delineated component of the renal parenchyma contains the glomeruli and much of the tubules.

Beneath the cortex are the distinctive renal pyramids whose bases abut the inner margin of the cortex and whose apices project into the lumens of the calyces. The pyramids are separated from each other by columns of cortical parenchyma. Linear striations converging at the apex reflect the confluence and directional drainage of the collecting tubule system.

The urine drains through the tubule pores at the pyramidal apices into cup-shaped calyces that conjoin at the renal pelvis. This structure empties into the ureter, which exits from the kidney at the medially oriented hilus.

Vasculature

One-fourth of the cardiac output passes through the glomeruli.

The renal arteries arise from the abdominal aorta and after a short course laterally enter the kidneys at the hilus. They rapidly divide in the renal pelvic area and send penetrating branches (interlobar arteries) between the pyramids. These, in turn, give rise to the arcuate arteries, which traverse the cortico–medullary junction running parallel to the kidney surface. From the arcuate arteries arise many branches that radiate through the cortex toward the renal capsule (interlobular arteries). These subdivide to form the many small afferent arterioles that supply the glomerular capillary plexus. The glomerular efferent vessels break up to form the microvascular network that passes through the interstitium to invest the tubules. (*Note:* Compromise of the afferent arteriole will therefore not only reduce the glomerular circulation but also affect the blood supply to the related tubules.)

The substance of the renal pyramids receives its blood supply from the efferent vessels of those glomeruli adjacent to the cortico–medullary junction. Venous drainage from the cortical and medullary interstitium follows the general pattern of the afferent arterial system and exits from the kidney at the hilus.

Histology

The nephron with its attendant microcirculatory system is the basic structural and functional renal unit. In simplified form it is an elongated tubule lined with cuboidal epithelium that originates with Bowman's capsule and its enclosed glomerulus and terminates at a collecting duct.

Glomerulus

This distinctive proximal extremity of the nephron is a complex capillary bed, interposed into a renal arteriole, which invaginates as a cluster of capillary loops into the thin, membranous, bulblike expansion at the beginning of the renal tubule.

As the afferent arteriole, which has no defined adventitia, enters the capsule, it immediately gives rise to several capillary loops. The functional "membrane" of this filtration apparatus consists of the endothelium, a relatively

thick, multilayered basement membrane, and the outer layer of attenuated visceral epithelial cells. These capillary loops rejoin to form the efferent arteriole as it exits from the glomerulus en route to supply the tubules.

The filtrate is collected in Bowman's capsule. The parietal surface of the capsule is lined by flattened epithelial cells that are in continuity with the proximal tubule epithelium at the capsule outlet.

Tubule

There are successive segments of the tubular portion of the nephron. The proximal convoluted tubule lies almost entirely within the cortex, the loop of Henle dips deeply into the medulla, and the distal convoluted tubule is once again in the cortical zone where it empties into a collecting tubule.

The fine structure and physiology of each segment are complex and will not be considered in detail except to reiterate that it is the responsibility of the tubule to resorb certain elements from the glomerular filtrate and actively secrete other metabolites.

Collecting Ducts

These simple tubules, as they traverse the medullary rays, receive urine discharged from the distal convoluted tubules. As they course in direct fashion down the medullary pyramids, they begin to merge until in the papillae they form large excretory ducts that empty into the calyces.

Interstitial Tissues

The basement membrane of the Bowman's capsules and tubules rests on a fine reticular interstitium through which courses the renal vasculature. This connective tissue is scanty under normal conditions and contains scattered fibroblasts and histiocytes.

CLINICAL SYNDROME

Although early experimental evidence had predicted the possibility of significant kidney damage associated with irradiation in the therapeutic range, it was generally considered that the kidneys were relatively unresponsive. Thus they were not initially accepted as a dose-limiting tissue in connection with radiotherapy of the abdomen. As more and more well-documented case reports came to light, the hazard of radiation-induced nephropathy became recognized, and more stringent and appropriate patient safeguards were adopted. This serious complication is rarely encountered in properly formulated and regulated therapy.

Early Acute Effects (During Therapy and Several Weeks Thereafter)

Unless the applied dose has been exceptionally large, seldom is any symptomatology ascribed to this very early phase of renal injury.

Laboratory analyses are usually inconsistent and equivocal. In this phase these analyses show the following: Renal blood flow and clearance may be initially elevated and then depressed toward the end of the therapy. Renal plasma levels fall progressively beginning at 450 rads. Glomerular filtration rate is depressed at 450 rads but elevated above preirradiation values between 550 and 1624 rads. It falls again below normal after 2000 rads cumulative dose and remains diminished for several months. Phenolsulfonphthalein test (PSP) and blood urea nitrogen (BUN) are normal. Although the specific gravity of the urine may be somewhat below normal, there is little or no albuminuria and no microhematuria.

Since this early period is usually without detectable evidence of renal injury, there is no definitive treatment. Furthermore, no measures presently available minimize or preclude the development of later phases of radiation nephropathy.

The silent nature of this acute injury precludes any reasonable assessment of the incidence of radiation nephritis as it relates to standard therapeutic regimens.

Early Delayed Effects (Several Weeks to Several Months After Irradiation)

Depending upon the degree of renal compromise, and therefore being roughly proportional to the size of the absorbed dose, the early clinical manifestations may be mild or severe and develop slowly or abruptly.

Clinical progression of the more severe forms of the early delayed nephropathy may be rapid with severe debilitation and possibly death within several weeks of onset.

Overt manifestations of early delayed nephropathy include

1. Edema of the lower extremities, which may become generalized in severe cases and be accompanied by pleural and/or peritoneal effusions.
2. Related hypertension, which can produce severe headaches, malaise, nausea and vomiting, and visual disturbances.
3. Enlargement of the heart over preirradiation radiographs.

Although the relatively short time (several months) between the onset of clinical evidence of renal-vascular compromise and abdominal radiotherapy favors radiation as the causative agent, other possible etiologies of this syndrome must be suspect and ruled out:

1. Renal disease unrelated to radiation.
2. The malaise, weakness, anemia, and ascites can be produced by metastases in the abdominal viscera.
3. The hypertensive headaches, vague neurological complaints, and papilledema can be mimicked by intracranial metastasis although the actual elevation of the blood pressure should be a convincing factor.

Laboratory analyses at this time will show the following: Renal function studies will reveal variable impairment. Urinalysis will show variable albuminuria and low specific gravity. Hyaline and granular casts and microhematuria may be present in the urine sediment. Hemogram will show variable (often severe) normocytic, normochromic anemia. All other formed blood components have essentially normal

values. The blood urea nitrogen will usually be significantly elevated and will continue to rise as the renal function compromise worsens. Contrast medium radiographs will generally be equivocal or normal.

Comment. As noted, there are two interdependent and interacting components of this nephropathy. On the basis of the relative intensity of the response in either the microvascular or epithelial structures, the clinical characteristics will resemble nephrosis or nephrosclerosis. Very often both are evident but with one or the other dominant.

TREATMENT. The less severe syndrome marked by variable depression of renal competence and mild to moderate hypertension is usually amenable to conservative patient care with bed rest; diet, electrolyte, and fluid restrictions; and specific drug administration.

Those individuals developing unusually severe renal-vascular nephropathy may rapidly succumb to renal failure and uremia or a malignant hypertensive state and congestive heart failure.

Late Effects (Several Months to Years After Radiotherapy)

This phase of radiation nephritis (late radiation nephropathy) depends upon the severity of the consequent progressive vascular sclerosis and the rapidity with which parenchymal ischemia develops.

The associated clinical syndrome may develop de novo in an insidious fashion, or there may be clinical indications of a preexistent or persistent renal functional deficit.

In instances of unilateral irradiation, the slowness with which this late nephropathy may evolve permits the contralateral kidney to hypertrophy and assume the additional burden of the failing irradiated organ. As a result, neither overt signs, nor symptoms may appear, and the true nature of the kidney damage may be viewed as an unexpected incidental finding many years later at surgery or autopsy.

When both renal beds have been irradiated, this compensatory factor is unavailable, and the renal functional capacity steadily declines.

In the milder form of late nephropathy, no consistent or explicit symptoms may occur; however, slight albuminuria, a reduction in specific gravity, and some granular and hyaline casts may be present. The blood urea nitrogen may be normal or slightly elevated. Frequently benign hypertension and anemia are present. An intravenous pyelogram may be helpful in identifying relative kidney atrophy.

In the severe responses the characteristics of the parenchymal damage will be reflected in the nature of the clinical syndrome. If the renal parenchymal atrophy is diffuse and severe, there will be progressive functional failure and uremia. If the vascular component of the late nephropathy dominates, those signs and symptoms relevant to hypertension will overshadow the renal deficit. It may be the insidious onset of hypertensive encephalopathy many years following radiation exposure that prompts the individual to seek medical assistance. Unless the history of abdominal radiotherapy is elicited, the etiology of the elevated blood pressure may not be appreciated.

Comment. Special mention should be made of the potential severe general debilitation that may be brought about by marked unilateral radiation nephropathy. As soon as the unirradiated kidney is determined to be capable of assuming the responsibilities of both organs, nephrectomy of the offending kidney can be a lifesaving procedure.

TREATMENT. As with all late changes associated with irradiation, those in the kidneys are irreversible and generally progressive.

The milder forms of late nephropathy may be helped by conservative management as indicated for the similar syndrome surfacing earlier in the postradiotherapy period. A prolonged and useful life may result.

Malignant hypertension developing in an individual with already compromised renal parenchyma has a grave prognosis. Death may occur within a few weeks of the onset of symptoms.

From the previous consideration of the clinical aspects of renal irradiation, many of the cases of "radiation nephritis" obviously may pass through more than one of the several indistinctly delineated syndromes. To look at this another way is to assume that all forms of this disease are indeed various phases or stages of the same basic nephropathy that either regresses or exacerbates at some point or points in relation to the time of the initial insult.

HISTOPATHOLOGY

Certain primary and metastatic tumors of the abdomen and contiguous tissues are treated by surgery with pre- or postoperative irradiation or by irradiation alone if the susceptibility of the tumor is appropriate or if surgical intervention is considered inadvisable. Of particular importance are those neoplasms which are relatively radioresponsive and thereby obtain an enhanced probability of growth control. Into this group fall testicular seminoma and its counterpart the infrequent ovarian dysgerminoma, lymphomas, and Wilms' tumor, or hypernephroma. Other malignancies, although not as radiosensitive, may exhibit enough beneficial radiation effect to warrant this form of therapy as an adjunct to surgery and chemotherapy. Consideration of the relative radiosensitivities of the diverse components of the renal parenchyma predicates the nature of the cytokinetic effect and the sequence in which these changes develop.

The two kidney-cell populations generally considered responsive to radiation are the endothelial cells, especially of the microvasculature, and the epithelium of Bowman's capsule and tubules. The latter is a relatively slow cell-renewal system.

Early Acute Effects

Under the circumstance of standard radiation therapy, no dramatic effect is expected during treatment or in the immediate posttherapy period. Transient injury to the fine vasculature of the glomeruli and to a less extent to that of the tubules may produce subclinical effects detectable only by careful sequential analytical studies.

Although there is rarely any opportunity to perform a detailed histologic evaluation during this very early phase, there are innumerable excellent mammalian experiments that can be conditionally extrapolated to man.

The following changes might be expected to develop:

1. Initial capillary congestion, especially in the glomeruli.

2. The endothelial cells become swollen, and protein-rich material passes readily into the subendothelial space forcing the endothelium away from the basement membrane.

3. There will be some degree of concurrent epithelial injury with random cells exhibiting swelling and/or degeneration.

The relatively slow elaboration of these early histopathologic effects and the slight to moderate degree of damage induced by therapeutic radiation levels do not exceed the functional tolerance of the kidney to any significant degree, hence, the clinically "silent" nature of this initial phase.

Be advised, however, that in this the stage has already been set for the possible evolution of a slowly progressive vascular sclerosis and associated degenerative parenchymal changes.

Comment. It is reasonable to assume that a very high proportion of individuals receiving even modest amounts of radiation to the kidney regions incur some degree of such transient and undetected nephropathy.

Early Delayed Effects

Most cases of acute radiation nephritis do not become clinically manifest for several months after the completion of the radiation therapy, which in itself belies the "acute" nature of this phase of radiation nephropathy. The related histopathology has been very slowly developing over a long period of time and involves not only the microvasculature but the arterioles and small arteries as well. The tubules and interstitium are secondarily affected by the microcirculatory disease. More pertinent and descriptive terms include nephrosclerosis, nephroglomerulosis, and the more comprehensive but cumbersome nephroglomeruloendotheliosis.

The more pertinent lesions include the following:

1. Variable constriction of the lumens of the afferent arterioles and glomerular capillary loops by subendothelial deposition of hyalin/fibrinoid substance.

2. Some degree of endothelial proliferation and possibly medial degeneration in small and medium arteries.

3. Variable interstitial edema and subsequent increase in the connective tissue. Increase of histiocytes and fibroblasts but no inflammatory infiltrate.

4. Tubule atrophy associated with those arterioles having significant occlusive disease. Some of the epithelial cells may be degenerative and pleomorphic as an indirect effect of the sclerosing nephrosis. There is minimal regeneration.

Some of these delayed radiation nephropathies will develop malignant hypertension. The histopathology will be significantly altered.

1. Glomerular degeneration (some may be spared) with thrombosis and hyalinization of the capillary loops. Bowman's capsule seldom shows proliferation or adhesions.

2. Endarteritis and necrotizing vasculitis involve primarily the afferent arterioles and not infrequently the interlobular arteries.

3. Arterial sclerosis and medial fibrinoid necrosis develop in the larger vessels.

Late Effects

The severely scarred, atrophic kidney commonly associated with late nephropathy should not be considered a separate entity. It is the end product of the very slow evolution of vascular sclerosis that eventually achieves a degree of parenchymal structural and functional compromise that is symptomatic and severely debilitating.

It is the product of a long-smouldering disease and differs in appearance from earlier stages only in the extensive atrophy and scarring.

1. The total mass of the kidney is usually greatly reduced owing principally to atrophy of nephrons.

2. The medium and large arteries are prominent as a result of the marked sclerosis.

3. The interstitium is wide and fibrosed but with minimal inflammatory infiltrate.

4. The kidney surface is irregular, and the capsule is thickened and fibrotic.

REFERENCES

Avioli, L. V., M. Z. Lazor, E. Cotlove, K. C. Brace, and J. R. Andrews, 1963, Early Effects of Radiation on Renal Function in Man, *Amer. J. Med.*, 34:329-337.

Jernigan, J. A., 1959, Chronic Radiation Nephritis, A Review of the Literature with a Report of a Case, *Ann. Intern. Med.*, 41:1084-1092.

Luxton, R. W. and P. B. Kunkler, 1964, Radiation Nephritis, *Acta Radiol.*, 2:169-178.

Madrazo, A., Y. Suzuki, and J. Churg, 1970, Radiation Nephritis: Chronic Changes After High Doses of Radiation, *Amer. J. Pathol.*, 61:37-54.

——, Y. Suzuki, and J. Churg, 1969, Radiation Nephritis: Acute Changes Following High Doses of Radiation, *Amer. J. Pathol.*, 54:507-527.

Maier, J. G., and G. W. Casarett, Patho-physiologic Aspects of Radiation Nephritis in Dogs, USAEC Report UR-626, University of Rochester, Apr. 8, 1963.

Mostofi, F. K., 1966, Radiation Effects on the Kidney, Chap. 16, in *The Kidney*, International Academy of Pathology, Monograph No. 6, F. K. Mostofi and D. E. Smith (Eds.), The Williams & Wilkins Company, Baltimore, Md.

Redd, B. L., Jr., 1960, Radiation Nephritis: Review, Case Report and Animal Study, *Amer. J. Roentgenol., Radium Ther. Nucl. Med.*, 83:88-106.

Rosen, S., M. A. Swerdlow, R. C. Muehrcke, and C. L. Pirani, 1964, Radiation Nephritis: Light and Electron Microscopic Observations, *Amer. J. Clin. Pathol.*, 41:487-502.

Rubenstone, A. I., and L. B. Fitch, 1962, Radiation Nephritis: A Clinicopathologic Study, *Amer. J. Med.*, 33:545-554.

Sagerman, R. H., Radiation Nephritis, 1964, *J. Urol.*, 91:332-336.

Schreiner, B. F., and R. M. Greendyke, 1959, Radiation Nephritis: Report of a Fatal Case, *Amer. J. Med.*, 26:146-151.

Van Slyck, E. J., and G. A. Bermudez, 1968, Radiation Nephritis, *Yale J. Biol. Med.*, 41:243-256.

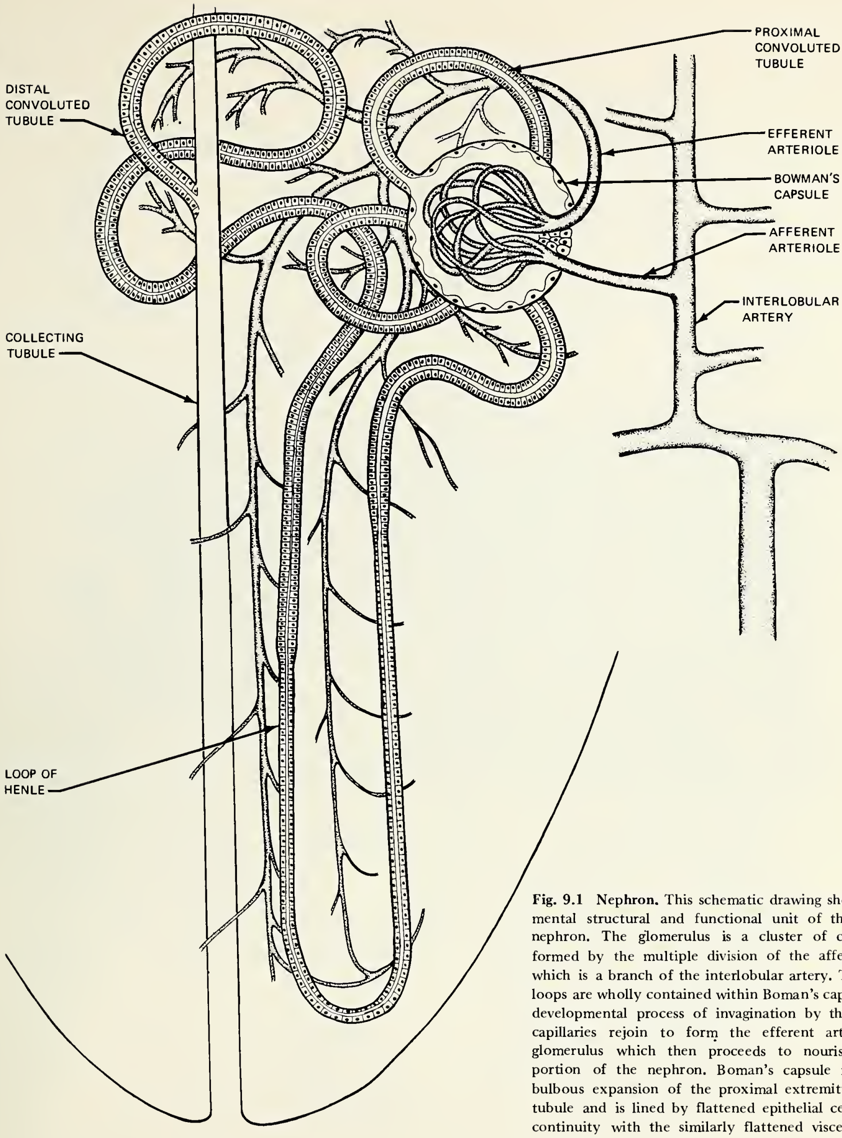
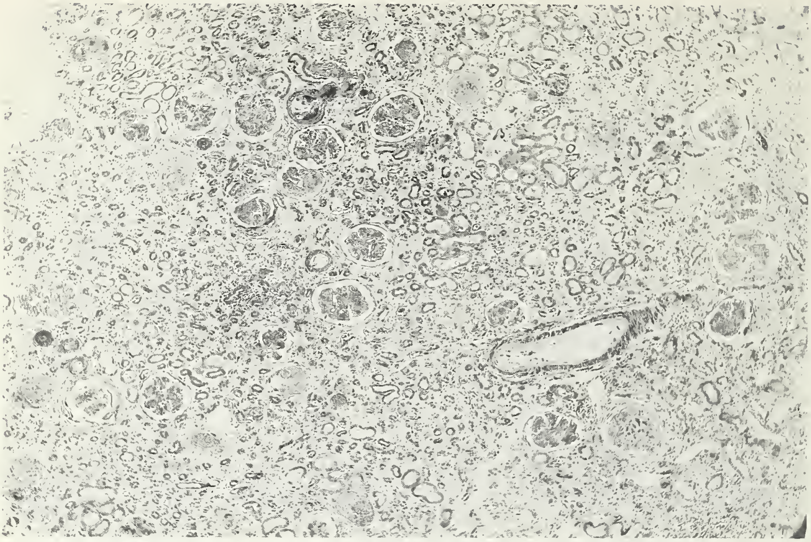


Fig. 9.1 Nephron. This schematic drawing shows the fundamental structural and functional unit of the kidney, the nephron. The glomerulus is a cluster of capillary loops formed by the multiple division of the afferent arteriole, which is a branch of the interlobular artery. These capillary loops are wholly contained within Boman's capsule through a developmental process of invagination by this plexus. The capillaries rejoin to form the efferent arteriole of the glomerulus which then proceeds to nourish the tubule portion of the nephron. Boman's capsule is in effect a bulbous expansion of the proximal extremity of the renal tubule and is lined by flattened epithelial cells that are in continuity with the similarly flattened visceral epithelium that invests the capillary loops and with the cuboidal epithelium of the tubule. There are successive segments to the tubule. The proximal convoluted portion exits from the capsule and lies wholly within the cortex. This is followed by the loop of Henle, which extends deeply into the medulla, and the distal convoluted tubule, which lies also in the cortex and discharges the filtrate into a collecting tubule.

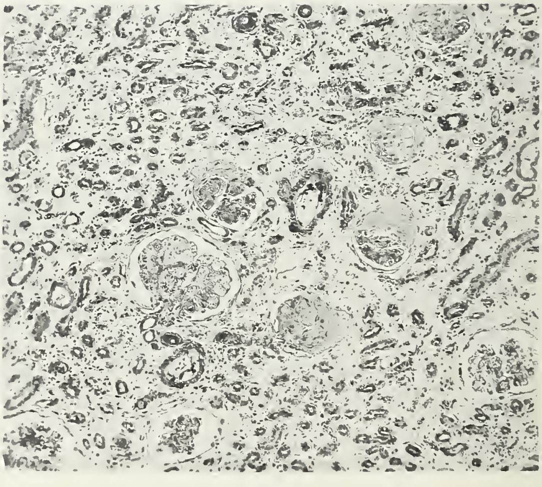
Fig. 9.2 Radiation responses in the renal parenchyma. Two cell types within the renal parenchyma are relatively responsive to radiation, i.e., the endothelium and the epithelium. It is not surprising, therefore, that essentially all the changes that develop in the renal tissue subsequent to irradiation are related in some manner to the anatomical and functional decrements produced in the endothelial and epithelial cells. This schematic diagram illustrates several possible effects that might become manifest in the early delayed radiation nephropathy. In the afferent arterioles damage to the endothelium will allow the transport of protein-rich substance into the subendothelial zone and media (A). This fibrinoid/hyaline accumulation associated with swelling of the endothelium and smooth muscle is capable of severely compromising the vessel lumen. This process may continue to spread and appear beneath the glomerular capillary endothelium (B). At the same time the basement membrane (C) displays significant thickening, and the visceral epithelial cells coating the capsular surface of the glomerular loops become swollen. This microcirculatory compromise has a tendency to promote thromboses (D) in the capillaries and may ultimately cause an infarct in part or all of the glomerulus. The tubule epithelium (E) will present a variable picture, with some cells having little or no visible change and others being pleomorphic and degenerative. On cross section some of the tubules will be dilated and may contain hyaline material, and many others will be atrophic and show a diminished cell count. There is usually some degree of interstitial fibrosis (F). As the vascular component of the delayed radiation nephropathy syndrome develops, even larger vessels may become affected. This medium artery discloses subendothelial connective-tissue proliferation with foci of necrosis and the presence of foamy histiocytes (G). The more exaggerated vascular changes are usually associated with those cases developing malignant hypertension.


F
D
B
E
C
A
G



(a)

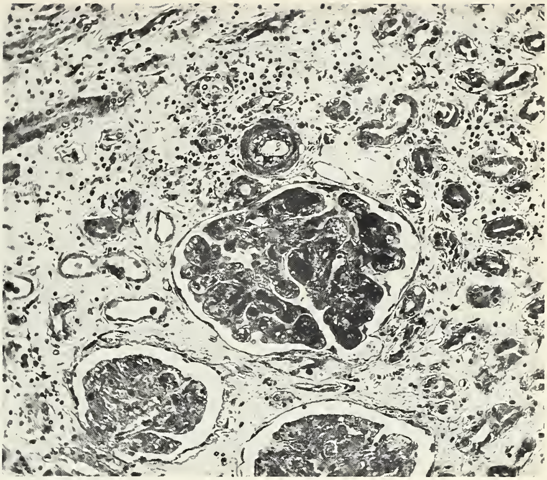
Fig. 9.3 Early delayed radiation nephropathy with hypertension. (a) In this low-power field of the renal cortex, the glomerular population is not significantly reduced, although several glomeruli are obviously in various stages of hyalinization. The vasculature is moderately prominent; most vessels show various types and degrees of structural change, most with luminal constriction. Interstitial fibrosis is moderately severe. Note that leukocytic infiltration is minimal.



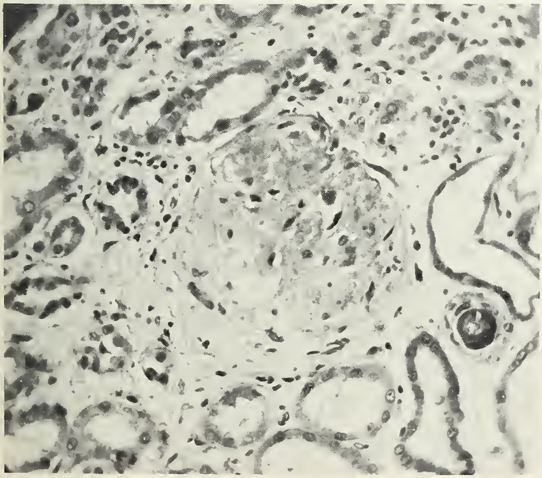
(b)

(b) The various phases of glomerular degeneration are evident in this field. The glomerulus in the lower right corner has an essentially normal appearance. The one in left center exhibits swollen, fused avascular tufts, such as in a bloodless infarct. The other glomeruli of this central cluster show partial to complete hyalinization. The vascular changes and interstitial fibrosis are severe.

(c) This glomerulus is for all practical purposes infarcted. The afferent arteriole has a lumen that has been reduced to near obliteration, the capillary loops are distended and engorged with red blood cells, and fibrin thrombi are present. The endothelium and visceral epithelium are indistinct and degenerative. Note the lack of capsule adhesions and the slight interstitial infiltration by lymphocytes and plasma cells.

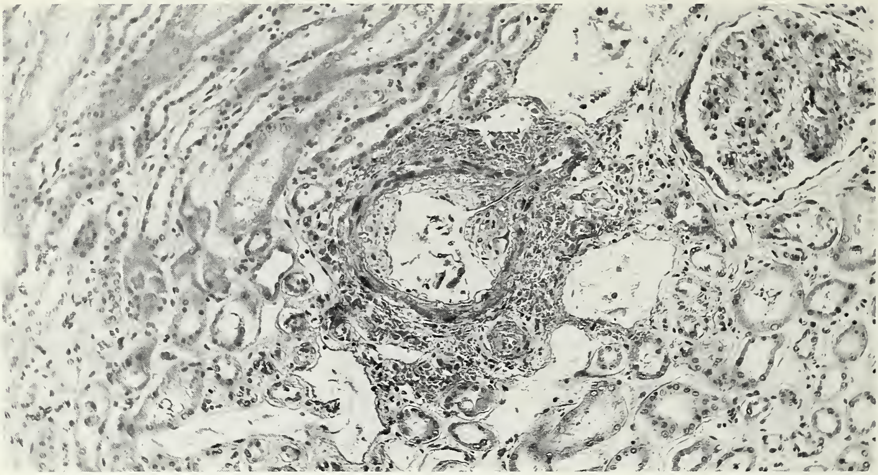


(c)



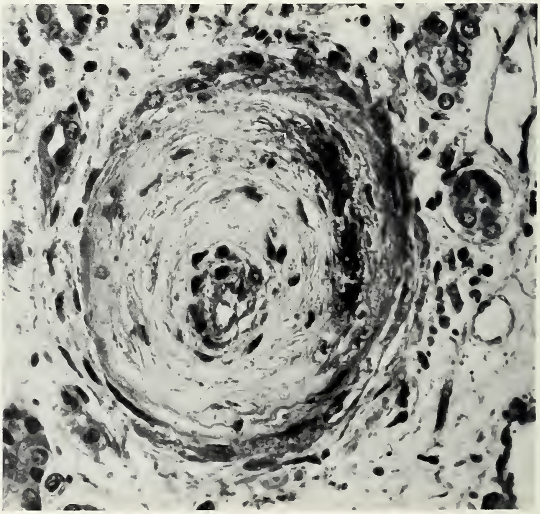
(d)

(d) The end stage of glomerular damage is illustrated in this high-power photomicrograph. The afferent arteriole, visible to the lower right of the glomerulus, has become totally occluded by the deposition of a dense hyaline substance in the subendothelial zone. In the glomerulus the fine capillary loops have been transformed into shapeless masses of dense hyaline-like substance containing entrapped degenerating cells of indeterminate type. A few foamy histiocytes are also caught up in these occluded tufts. Bowman's space has been obliterated although the degree of actual capsular thickening is relatively slight.



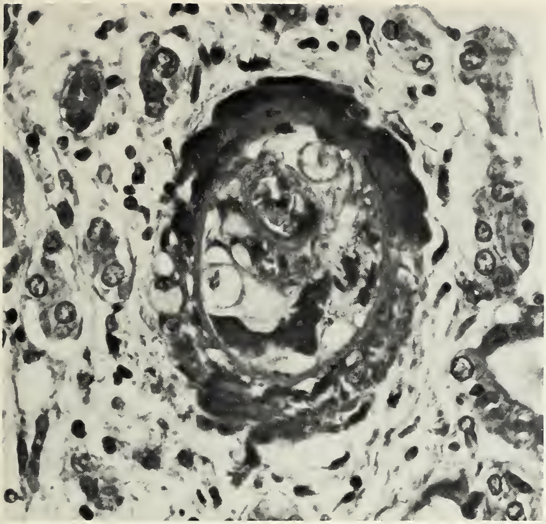
(a)

Fig. 9.4 Vascular changes in delayed radiation nephropathy. (a) The variant of delayed radiation nephropathy associated with severe or malignant hypertension has distinctive arterial and arteriolar changes. The medium artery in the center of this photomicrograph displays primarily an asymmetrical subendothelial connective-tissue proliferation, which in this section has effectively obliterated the orifice of a small branch emanating from the upper-right quadrant of the artery.



(b) This high-power photomicrograph of a medium artery shows severe constriction of the lumen by marked proliferation of the subendothelial connective tissue. To the right of the lumen and just within the elastica interna is a zone of degeneration with deposition of protein-rich substance and some lipid.

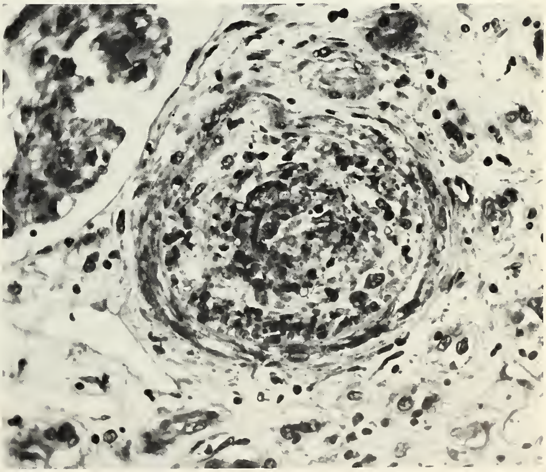
(b)



(c)

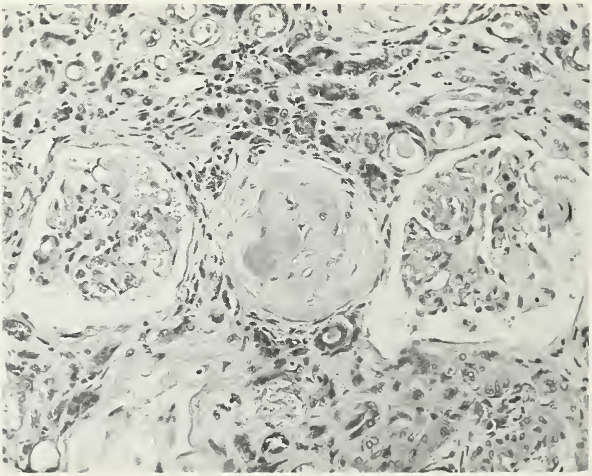
(c) Frequently, a combination of subendothelial proliferation, zonal necrosis, and deposition of fibrinoid and hyalinoid substance can effectively compress the vessel lumen. In this vessel there is degeneration in both subendothelium and medial zones with deposition of irregular dense masses of homogeneous material. Between the elastica interna and the endothelium are many swollen, foamy histiocytes.

(d) Hemorrhage into a segment of necrotizing vasculitis may precipitate a sudden occlusion of the lumen. Most of the endothelial and myothelial cells that comprise the vessel wall are degenerative. The lumen is indistinct in this photomicrograph but centrally situated.



(d)

Fig. 9.5 Late delayed radiation nephropathy. **(a)** In these kidneys the vascular sclerosis dominates the picture and usually involves all vessels up to and including the renal artery. The duration of this disease has resulted in a reduction of total kidney mass primarily because of glomerular and tubular atrophy and condensation of the interstitial fibrosis. Although a few random glomeruli may be almost normal in appearance, the majority will have some degree of hyalinization. The medium and large arteries are particularly prominent in that they display marked intimal and medial thickening. The tubules will range from cystic dilatation to almost total atrophy.



(b) This high-power photomicrograph shows three glomeruli. The central glomerulus is completely hyalinized with obliteration of the capsule space and no delineation of the glomerular structure. The flanking glomeruli exhibit focal hyaline deposition in portions of the glomerular tufts. There are no capsular adhesions in these latter structures. Note the severe adjacent interstitial fibrosis and tubule atrophy.

Chapter 10
Urinary Bladder and Prostate

URINARY BLADDER

Normal Structure and Function

All segments of the extrarenal excretory tract (calyces, pelvis, ureter, and bladder) have a basic similarity of structure (mucosa and lamina propria, smooth-muscle layers, and adventitia) and a singularity of purpose (i.e., transporting the urine outside the body).

MUCOSA. The mucosa consists of transitional epithelium that is four to five cell layers thick in the ureters and six to eight cell layers thick in the empty, contracted bladder. It is impermeable to the soluble substances of normal urine. There are no true mucosal glands except in the vicinity of the urethral orifice. These small, sometimes branched glands are lined with clear mucus-secreting cells and are situated at the bases of deep mucosal invaginations. There is no defined basement membrane.

LAMINA PROPRIA. The lamina propria has dense elastic and collagen fibers, small lymphatic nodules, and a plexus of vessels and nerve radicles. In the bladder the lamina is quite thick.

MUSCLE LAYERS. In the bladder are three muscle layers that are not always distinctly delineated: (1) The inner layer consists of irregularly distributed longitudinal and oblique fibers. This layer also makes up the internal sphincter of the urethra. (2) The middle layer has circular and spiral fibers and is the thickest of the three. (3) The outer longitudinal muscle layer is well-developed over the dorsal and ventral aspects; however, the fibers are fewer and more discontinuous laterally.

The ureters penetrate the bladder wall at an angle such that the pressure of the fluid within the bladder tends to keep ureterovesical orifices closed. A mucosal fold also helps to form a valve-like structure.

In general, it may be said that the muscle bundles of the urinary bladder are not as compact or uniform in structure as, for example, the esophagus or intestine. Furthermore, there is a relative abundance of loose connective tissue trabeculae.

Clinical Syndrome

Radiation cystitis is an all-inclusive term commonly applied to both acute and chronic conditions stemming from the irradiation of primary bladder tumors or the treatment of malignancies in contiguous tissues, e.g., uterus and vagina.

EARLY EFFECTS. 1. Symptoms include dysuria, frequency, and nocturia.

2. The capacity of the bladder progressively diminishes.

3. Cystoscopy discloses diffuse hyperemia, partial desquamation of mucosa, and possible focal ulceration.

4. This inflammatory response usually regresses within a few weeks after completion of the therapy.

5. If a relatively radioresponsive tumor has replaced a focal area of the bladder wall, acute destruction of this neoplasm may produce a deep ulcer with the possibility of perforation.

DELAYED EFFECTS. 1. Painless hematuria appearing several months after the radiotherapy often signals the development of a trigonal ulcer.

2. Cystoscopic examination usually discloses an area of mucosal atrophy and scarring on the posterior bladder wall with the ulcer situated in the area of greatest tissue compromise.

3. There is often a concurrent bladder infection, which may become symptomatic.

4. The superimposition of inflammation and edema in an already fibrosed bladder wall may cause blockage of the mural ureters and a hydroureter/hydronephrosis.

5. Prompt treatment of the inflammatory condition may abort or reverse a developing uremia.

LATE EFFECTS. 1. Symptoms are slowly developing frequency and nocturia appearing 1 to 5 years after the radiation therapy.

2. Cystograms and cystoscopy reveal a very contracted bladder with prominent trabeculations.

3. The consensus is that this debilitative condition arises from combined etiologies, e.g., irradiation and infection, invasive tumor, and irradiation and scarring.

4. May cause ureteral obstruction which is refractive to conservative treatment and which may require translocation. It should be pointed out that ureteral stricture on the basis of radiation alone is uncommon.

Radiation Histopathology

EARLY EFFECTS. 1. Degeneration of radioresponsive cells in the basal layer of the epithelium and suppression of cell division.

2. Failure to replace epithelial cells lost through attrition, and direct radiation death may result in denudation of mucosa.

3. Vascular congestion and edema.

4. Early damage to the microvasculature, which may produce a relative transient ischemia in the dependent tissues and amplify direct effects.

5. A combination of the above effects may result in the formation of mucosal ulcers. These ulcers are often coated with an adherent fibrinopurulent exudate.

DELAYED EFFECTS. 1. Resurfacing of acute ulcers by proliferating epithelium. Usually atrophic but with areas of hypertrophy.

2. May be progressive focal sclerosis in arterial and arteriolar walls and variable telangiectasia.

3. Increasing fibrosis of lamina and muscle layers. Presence of "radiation fibroblasts." These must be distinguished from the multinucleated cells often associated with a chronic cystitis.

4. The above changes will increase the susceptibility of the mucosa to intercurrent trauma and/or infection. Secondary ulcerations may develop which are more deeply penetrating and more difficult to heal.

LATE EFFECTS. 1. Continued fibrosis of entire thickness of bladder wall.

2. Continued vascular sclerosis with depression of functional efficiency of all supportive components.

3. Ulcerations and rupture of superficial telangiectatic vessels may produce repeated episodes of hematuria.

4. Possibility of fistula formation as a result of the above.

PROSTATE

Normal Structure and Function

The prostate is classically described as the size of a chestnut. It is a firm, musculoglandular organ located beneath the internal urethral orifice and enclosing the proximal portion of the urethra. It consists of an abundance of compound tubulo-alveolar glands that excrete a thin opalescent, slightly alkaline fluid via numerous ducts into the urethra. The glandular epithelium is, for the most part, simple or pseudostratified columnar in type; however, epithelia of cuboidal or even squamous varieties are not unusual.

These glands have no distinct basement membrane; therefore the lining cells appear to rest directly upon the contiguous dense connective tissue. The interstitial tissue is abundant and forms broad interlacing bands of smooth muscle and dense connective tissue. About the urethra the smooth-muscle cells and elastic fibers form a collar, which is the internal sphincter. The whole of the gland is encased by a peripheral zone of compact fibrous tissue.

Clinical Syndrome

There are no specific signs or symptoms relating to irradiation of the normal prostate gland. This structure is considered to be relatively unresponsive to radiation even at high doses given in standard fractions and weekly doses of 1000 to 1200 rads.

There is no evidence that the incidental irradiation of this organ in the course of treating bladder tumors has ever produced a clinically significant early response, e.g., edema with urethral obstruction. Further, any late delayed response, such as fibrosis and variable glandular atrophy associated with vascular sclerosis, is not likely to evoke any symptoms.

Radiotherapy of Prostatic Carcinoma

In view of the relative lack of response of the normal prostate to radiation, attention should be directed toward the potential benefits to be derived from the radiotherapy of prostate adenocarcinoma and the problems associated with this mode of treatment.

Prostatic cancer ranks second only to lung cancer in prevalence, and, in spite of its reputed relative low-grade malignant nature, accounts for about 9% of all cancer deaths in the male (ranks fifth). It should be noted here, however, that some of these carcinomas are poorly differentiated and grow rapidly with early metastasis. Because the slow growth of most of these tumors does not generally produce any symptoms until there is (1) obstruction of the proximal urethra or (2) effects from metastases (especially bony), most prostate cancers when detected have already invaded the gland bed and beyond. Nevertheless there is merit in establishing clinical grading of the lesion if only to assist in the selection of a treatment program that is best suited for tumor control.

One such staging is summarized as follows:

Stage A: Lesions that are occult and are found incidentally on pathological evaluation of a transurethral resection specimen or at autopsy.

Stage B: This carcinoma is entirely contained within the prostatic capsule and is relatively small. These can sometimes be palpated by rectal examination, although over half these lesions are in the lateral and anterior aspects of the gland and are difficult to detect.

Stage C: Lesions that have invaded the capsule and have penetrated into the adjacent connective tissues, seminal vesicles, bladder, and urethra. Also included in this category are those primary carcinomas of very large size which apparently are still contained within the capsule.

Stage D: This stage has detectable vascular and lymphatic extension and demonstrable bony or extrapelvic involvement.

Optimum patient care depends on a comprehensive clinical and laboratory evaluation for the selection of the most appropriate treatment regime. Certain generalities apply, however:

1. A radical prostatectomy must be considered the treatment of choice in most instances, although less than 10% of the candidates qualify.

2. Most patients are already stage C or D when evaluated.

3. Castration or the administration of estrogens has only a limited value in the management of patients with metastatic symptomatic disease.

4. Supervoltage radiation therapy, especially as applied by rotational techniques, has greatly improved the intensity and definition of the depth dose with significant sparing of contiguous normal tissues. It shows promise as an effective means of tumor control in certain stage A to C cases.

5. Interstitial irradiation, particularly that using gold (^{198}Au) with its strong emission of beta rays and some gamma radiation, has been used effectively in certain selected cases: (a) in localized lesions where radical surgery is precluded and (b) in the bed of the prostatectomy where penetration of the capsule is suspected or known. It is conceded, however, that this mode of therapy does not produce a uniform radiation field and will not control metastatic tumor in proximal nodes.

It should be pointed out that the reputation of the well-differentiated prostatic adenocarcinoma as being "radioresistant" is based on the fact that it reacts slowly to the effects of radiation in contrast to the rapid dissolution of certain fast-growing so-called "sensitive" tumors under comparable circumstances of radiotherapy. This slow response time has no real bearing on a specific tumor's radiocurability.

Regardless of the mode of treatment selected, the most encouraging results will emanate from centers that are particularly qualified in either radical surgery or controlled irradiation.

Radiation Histopathology

There has been very little descriptive information reported relevant to the tissue response to radiation.

1. The cells of the adenocarcinoma will exhibit morphologic changes earlier than the adjacent normal epithelium.

2. The malignant cells will show swelling of nucleus and cytoplasm with increased homogeneity to the chromatin. These cells may slough at this point or become pyknotic and disintegrate.

3. Nonmalignant epithelium is less responsive but may ultimately display some pleomorphism and even metaplasia.

4. There will be late-developing progressive vascular sclerosis and associated increased dense fibrosis and glandular atrophy.

REFERENCES

Urinary Bladder

Alfert, H. J., and J. Y. Gillenwater, 1972, The Consequences of Ureteral Irradiation with Special Reference to Subsequent Ureteral Injury, *J. Urol.*, **107**: 369-371.

Bloedorn, F. G., J. D. Young, C. A. Cuccia, R. Mercado, Jr., and M. J. Wizenberg, 1962, Radiotherapy in Carcinoma of the Bladder: Possible Complications and Their Prevention, *Radiology*, 79: 576-581.

Dean, A. L., and D. P. Slaughter, 1941, Bladder Injury Subsequent to Irradiation of the Uterus, *J. Urol.*, 46: 917-924.

Fletcher, G. H., T. C. Brown, and F. Rutledge, 1958, Clinical Significance of Rectal and Bladder Dose Measurements in Radium Therapy of Cancer of the Uterine Cervix, *Amer. J. Roentgenol., Radium Ther. Nucl. Med.*, 79: 421-450.

Gowing, N. F. C., 1960, Treatment of Carcinoma of the Bladder. III. Pathological Changes in the Bladder Following Irradiation, *Brit. J. Radiol.*, 33: 484-487.

Hueper, W. C., C. V. Fisher, J. deCarvajel-Forero, and M. R. Thompson, 1942, The Pathology of Experimental Roentgencystitis in Dogs, *J. Urol.*, 47: 156.

Kurohara, S. S., P. Rubin, and N. Silon, 1965, Analysis on Depth of Bladder Cancer Treated by Supervoltage Therapy, *Amer. J. Roentgenol., Radium Ther. Nucl. Med.*, 95: 458-467.

Mallik, M. K., 1962, Study of Radiation Necrosis of the Urinary Bladder Following Treatment of Carcinoma of the Cervix, *Amer. J. Obstet. Gynecol.*, 83: 393-400.

Masterson, B. J., and F. Rutledge, 1967, Irradiation Ulcer of the Urinary Bladder, *Obstet. Gynecol.*, **30**: 23-27.

Morrison, R., and T. J. Deeley, 1965, The Treatment of Carcinoma of the Bladder by Supervoltage X-Rays, *Brit. J. Radiol.*, **38**: 449-458.

Watson, E. M., C. C. Herger, and H. R. P. Sauer, 1947, Irradiation Reactions in the Bladder: Their Occurrence and Clinical Course Following the Use of X-Ray and Radium in the Treatment of Female Pelvic Disease, *J. Urol.*, 57: 1038-1049.

Prostate

Bagshaw, M. A., 1969, Definitive Radiotherapy in Carcinoma of the Prostate, *J. Amer. Med. Ass.*, **210**: 326-327.

Barnes, R. W., 1969, Survival with Conservative Therapy, *J. Amer. Med. Ass.*, **210**: 331-332.

DelRegato, J. A., 1967, Radiotherapy in the Conservative Treatment of Operable Carcinoma of the Prostate, *Radiology*, **88**: 761-766.

Flocks, R. H., 1969, Present Status of Interstitial Irradiation in Managing Prostatic Cancer, *J. Amer. Med. Ass.*, **210**: 328-330.

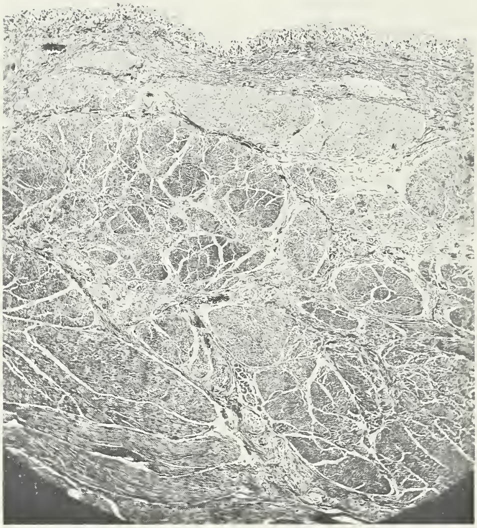
George, F. W., C. E. Carlton, Jr., R. F. Dykhuizen, and J. R. Dillon, 1965, Cobalt-60 Telecurietherapy in the Definitive Treatment of Carcinoma of the Prostate: a Preliminary Report, *J. Urol.*, 93: 102.

Jewett, H. J., 1969, The Results of Radical Perineal Prostatectomy, *J. Amer. Med. Ass.*, **210**: 324-325.

Loh, E. S., H. E. Brown, and D. D. Beiler, 1971, Radiotherapy of Carcinoma of the Prostate: Preliminary Report, *J. Urol.*, 196: 906.

Mannion, R. A., 1974, The Negative Effects of Supervoltage External Irradiation in Prostatic Carcinoma: Report of 2 Cases, *J. Urol.*, **111**: 75-76.

Rubin, P., 1969, Supervoltage Radiation Therapy—Promise Vs. Fulfillment, *J. Amer. Med. Ass.*, 210: 333-334.



(a)

Fig. 10.1 (a) This low-power photomicrograph illustrates most of the structure of the bladder wall. The inner lining is transitional epithelium several cell layers deep. The underlying lamina propria is composed of dense collagen and elastic fibers and contains a rich plexus of small blood vessels and lymphatics. Muscle layers comprise the bulk of the bladder wall and are indistinctly delineated into an inner layer of longitudinal and oblique fibers, a medial zone of circumferential and spiral fibers, and an outer layer of longitudinal muscle.

(b)

(b) This low-power view shows late changes in the irradiated bladder. The surface is denuded, and the lamina propria is necrotic and "shaggy" with congested vessels. Fibrous tissue has replaced most of the muscle with an edge of a "punched-out" ulcer appearing at the right edge of this section. Large sclerotic arteries are present in the outer muscle region.

(c)

(c) Necrosis of the bladder wall is more severe in this section and extends almost through the wall. The bladder surface has no residual epithelium, and there is only a narrow lamina propria at the right edge of this photograph. The surface is coated with a very thick layer of necrotic tissue and fibrin. The muscle layers are moderately atrophic and show severe fibrosis.

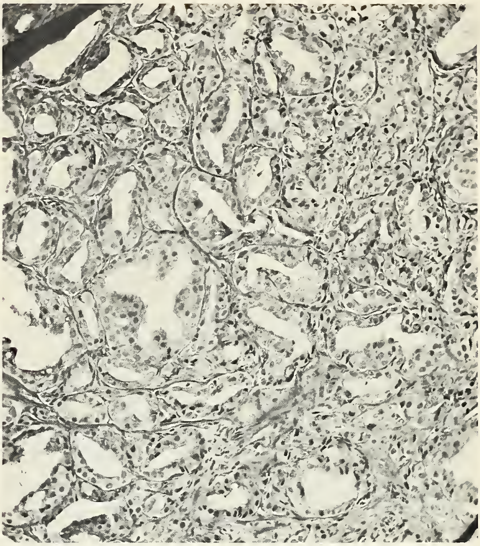
(a)

Fig. 10.2 (a) The prostate is a musculoglandular organ situated at the proximal end of the urethra. This low-power photomicrograph is taken at the vesicourethral junction and illustrates the smooth-muscle fibers that encircle the internal sphincter in this vicinity. In the gland proper is glandular hyperplasia with interlacing and encircling bands of muscle and dense connective tissue.

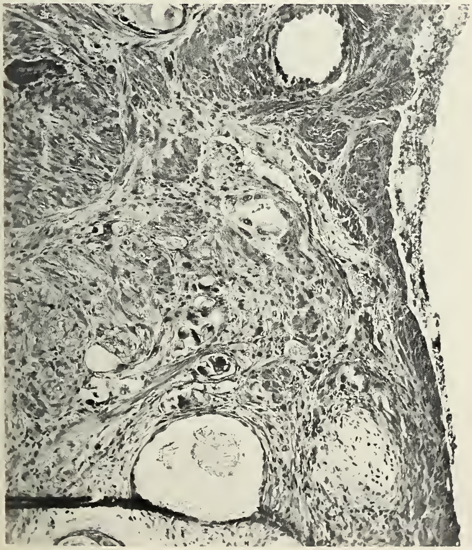
(b) Irradiation of the prostate seldom produces any early changes but may result in atypical epithelium and increased interstitial fibrosis as delayed responses. The residual fragment of mucosa is squamous in appearance with some cell pleomorphism. A similar metaplastic change is evident in some of the glands. Muscle fibers are separated by fibrous trabeculae.

(b)

(c) This section illustrates a pretherapy prostate biopsy with moderately well differentiated adenocarcinoma.



(c)



(d)

(d) Megavoltage sources now permit the concentration of intense irradiation in the prostate with greatly reduced exposure of sensitive contiguous structures, such as rectum and bladder. This posttherapy biopsy illustrates advanced degenerative changes in the cancer-cell aggregates with notably less effect in adjacent normal glands (top and bottom).

Chapter 11
Uterus and Vagina

NORMAL STRUCTURE AND FUNCTION

The uterus is a roughly pear-shaped, thick-walled muscular organ that is virtually suspended in midposition in the pelvic concavity by a series of paired ligaments and attachments to the urinary bladder anteriorly and rectum posteriorly. It has a mucosa-lined central cavity expanded at the superior pole into two blunted "horns" which communicate directly with the fallopian tubes. The distal end opens through the cervix into the vaginal vault.

It is convenient to identify at least three parts of the uterus: (1) The body or corpus of the uterus with the rounded superior pole or fundus; (2) the isthmus, which is the narrowed middle segment; and (3) the cervix or distal segment, which contains the endocervical canal. The portio vaginalis is that part of the cervix which protrudes into the vaginal vault.

The wall of the uterus has three distinct layers: (1) The inner mucous membrane, (2) the thick middle layer (almost entirely smooth muscle in the body and isthmus and mostly dense fibrous tissue in the cervix), and (3) the serous membrane, which is present only over that portion of the uterus which protrudes into the peritoneal cavity.

Mucosa

1. *Endometrium* (subject to complex cyclic change associated with ovarian activity during the reproductive period): Surface and tubular glandular epithelium (simple columnar type) and stroma (loose mesenchymal-like connective tissue).
2. *Isthmus* (little or no cyclic change): Glandular structures infrequent and stroma more dense.
3. *Cervix—endocervix* (no alteration with menses): Tall, columnar epithelium with numerous branching, mucosecreting glands that change abruptly to a stratified squamous epithelium on the portio vaginalis of the cervix. Stroma is very dense but well vascularized.

Myometrium

The myometrium contains interlacing bands and bundles of smooth-muscle cells with connective tissue (collagen fibers, fibroblasts, and elastic fibers); the proportion of dense fibrous tissue which increases as the portio vaginalis is reached.

Serous Membrane

The serous membrane is a reflection of the peritoneum, which encases only a portion of the uterus.

CLINICAL CORRELATION

Behavior of Carcinoma of Cervix

1. Carcinoma of the cervix initially appears in the area about the squamocolumnar junction of the endocervix or at the cervical os.

2. The primary site may be exophytic, plaque-like, ulcerative, or occult.

3. May invade early or late.

4. Extension usually involves the lateral fornices, less frequently the anterior fornix, and rarely the posterior fornix.

5. Extension may also occur upward into the wall of the isthmus.

6. Direct extension to structures other than the uterus: Vaginal walls (usually late), bladder (occurs after vaginal invasion), rectum (occurs after vaginal invasion), and parametrium (early and often).

7. Metastases to lymph nodes: The relative degree of lymph-node involvement is very difficult to determine with any degree of accuracy. There is no set pattern insofar as sequence of lymph-node involvement is concerned. Treatment must be directed at all groups of nodes draining this structure.

8. Clinical staging of cervical malignancy as a form of pretherapy classification is mainly a subjective evaluation and open to considerable variation in interpretation: This is one factor in the wide range of 5-year control rates reported by stage classification. Staging has limited application in preliminary case assessment. Malignant cells were found in pelvic nodes in about 16.5% of stage 1, 3.9% of stage 2, and 46.7% of stage 3.

Behavior of Carcinoma of Endometrium

1. Carcinoma of the endometrium is one-fifth as frequent as carcinoma of the cervix and usually occurs postmenopause.

2. Frequently remains confined to the mucosal bed for long periods and extends and metastasizes slowly in comparison with the cervical carcinoma.

3. Preoperative radiation applied to either eradicate the tumor or minimize possible seeding of viable malignant cells during subsequent surgery.

4. Although preoperative irradiation can destroy viable tumor in 50% or more of involved uteri and radium alone can produce 5-year apparently tumor-free survivals in 53% of unselected cases, it is quite apparent that there are some instances of endometrial carcinoma which will be resistant to the actions of radiation but may be successfully and totally extirpated by surgery. Conversely, clinically localized carcinomas may have early undetected extension into the parametrium beyond the limits of safe surgery but nevertheless readily controlled by external pelvic irradiation.

Rationale for Combined Therapy

The contact application of radium or its equivalent will provide a mucosal dose of 15,000 to 30,000 rads. Because of the very rapid attenuation over a relatively short tissue distance, there will not generally be a cancerocidal dose beyond 3 to 3.5 cm from the point of greatest radioactivity. The nature of the spread of the malignancy requires that the corpus of the uterus, the upper vagina, the parametria and ligaments, and the regional lymph-node groups receive cancerocidal amounts of radiation. Avoidance of superimposed radiation in tissues already treated to maximum tolerance is best accomplished by carefully directed multiple beams of external radiation with appropriate shielding of the midline structures.

RADIATION HISTOPATHOLOGY

Suitability to Radiation Therapy (General Considerations)

1. Ready access for the contact application of radioactive materials without direct incursion of body tissue or penetration into peritoneum.

2. With the exception of the apposed rectum, there is no critical and sensitive tissue that would exert excessive restriction on the quantity of radiation imposed locally.

3. Capacity of the cell-renewal epithelium to recover to some degree.

4. Abundant vascularity helps to minimize any ischemic effects that might be produced by radiation thickening of the vessel walls.

5. The wall of the uterus is relatively unresponsive to high doses of radiation.

6. Loss of the function of the uterus and, for that matter, the adjacent ovaries is of little consequence in relation to the attempted ablation of the malignancy.

7. Diagnosis and sequential evaluations of therapeutic efficacy are performed with relative ease.

8. The effects of the therapeutic irradiation do not significantly alter the feasibility and desirability of adjunctive surgery and, for that matter, often improve the operability.

9. Any clinical observations suggestive of tumor recurrence should be followed promptly by resection even in the absence of pathological corroboration.

Histopathology

EARLY EFFECTS. 1. Loss of mitotic activity in the cell-renewal systems of the mucosa (squamous and glandular epithelia).

2. Direct cell damage as well as mitosis-connected changes that will produce atypical cell forms having variably shortened life-spans and reduced functional states.

3. Extended delay in cell regeneration or a drastically reduced mitotic rate may result in focal denudation of the mucosa.

4. Loss of this protective epithelial barrier provides entry for pathogens with resultant inflammation and ulceration.

5. The supportive compartment of the submucosa will exhibit edema, swelling of collagen and elastic fibers, and endothelial and myothelial swelling in the vessels with some variable relative, focal tissue ischemia.

6. If radium capsules have been used, the dose to the apposed tissues will be so great that there will be rapidly developing superficial coagulation necrosis with underlying hyaline degeneration. Few, if any, viable cells will remain in this well-circumscribed area of intense tissue injury. *Comment:* This narrow zone of intense tissue destruction is often seen histologically as very sharply demarcated from the underlying stroma. The reason for this effect probably lies in the composition of the radium capsule. The usual wall filtration is 0.5 mm of platinum, which affects the emanating radiations as follows:

- (a) *Gamma:* Average energy is 0.83 MeV with a dose rate of 8.25 R/hr/mg at 1.0 cm.
- (b) *Alpha:* All alpha is absorbed by the capsule wall.
- (c) *Beta:* The range of this radiation is 0.53 mm in platinum. Thus, if the capsule wall is unusually thin (0.2 or 0.3 mm of gold or platinum), many beta rays will penetrate the capsule to extend a short distance into the tissue. For the 0.5-mm wall, the amount of penetration would be very small (1% of that contributed by the energetic gamma radiations).
- (d) *Secondary electrons:* These electrons produced in the capsule wall contribute substantially to the radiation dose at the applicator–tissue interface, but this type of radiation falls off abruptly beyond 1 mm of tissue penetration.

DELAYED EFFECTS. 1. If the proliferative capacity of the stem-cell component has not been nullified by the radiation, resurfacing of the mucosa will be accomplished rather rapidly by the regenerating epithelium.

2. In the submucosa the more severely altered connective-tissue elements will persist. Some of the fibroblasts may be greatly enlarged and pleomorphic. Fibrosis of the damaged tissues will develop.

3. Although much of the endothelial swelling was of a transient nature, the protracted or intermittent exposures may have produced significant thickening of the vessel walls, which may persist and become even more severe with time. Because of the great vascularity of the uterus, this usually will not result in a significant degree of ischemia.

4. Telangiectasia of the superficial vessels may develop.

5. As might be expected, the malignant counterparts of the epithelia respond in a similar fashion but do not have the same propensity for recovery.

6. With sufficient lapse of time, those few residual viable tumor cells will recover and resume their active and uncontrolled proliferation. This recovery in a graded form can be observed in a deeply penetrating tumor treated primarily with radium. The drop-off in cancerocidal isodose patterns is readily observed.

7. In a few cases an excessive quantity of radiation may be absorbed by the rectovaginal and vesicoureteral junctions with the development of severe proctitis or cystitis. Acute rectovaginal and vesicovaginal fistulas may occur.

LATE EFFECTS. 1. The usual treatment program for carcinoma of the uterus calls for surgical removal at some relatively early time subsequent to the completion of the radiotherapy. Very late effects of radiation are, therefore, not often seen.

2. In inoperable cases the spread of the malignancy will mask much of the change produced by the radiation.

3. The cervix will be fibrotic with severely thickened vessels and some superficial telangiectasia. There is often an associated inflammatory infiltrate consisting primarily of lymphocytes, monocytes, and plasma cells. The overlying epithelium is usually atrophic with variable degrees of cell pleomorphism.

4. The corpus will exhibit many similar alterations with fingers of fibrous tissue extending down into the myometrium. The mucosa will be shallow and atrophic with resting glands few in number and widely spaced owing to the direct action of the radiation plus the radiation-induced ablation of hormonal cyclic changes. If radium capsules were used, there may be focal areas of hyaline degeneration, which may or may not be surfaced by a layer of epithelium.

Limiting Anatomical Factors

The relative reactivity of the contiguous structures is as follows:

1. *Rectum* (most prone to direct radiation injury): relatively fixed position, proximity to vaginal radium, and responsiveness of rectal epithelium and microvasculature.

2. *Small bowel:* Mobility minimizes dose absorbed by any single segment. Previous pelvic or intra-abdominal surgery or peritoneal inflammation may affix a segment of small bowel in the deep pelvis where it will receive much the same dose as the rectum.

3. *Bladder:* Endometrial radium capsules are the principal offenders, especially when there is anteflexion of the uterus. The bladder is not infrequently subject to acute cystitis due to response of epithelium and microvasculature. The most severe sequelae are related to invasion of the bladder wall by malignancy with superimposed radiation effects.

4. *Ureters:* By anatomical location (within 1 to 2 cm of lateral fornices and cervix) should be susceptible to effects of therapy. Remarkably resistant to direct radiation injury, although external compression from scarring and tumor may diminish lumen.

5. *Skin, soft tissues, and femoral head and neck:* No longer considered a major problem in therapy because of increased beam energies and more carefully controlled regimes.

Comment: Clinicopathologic implications concerning the use of radiation preoperatively (which is the usual method of combined treatment).

1. Reduce the number of viable tumor cells at the primary site so that there is less chance of vascular infusion of malignant cells and peritoneal seeding of cells at the time of surgery. It is possible that all the tumor may have been eradicated by the radiation alone.

2. Render any residual tumor cells incapable of continued proliferation.

3. Sclerosing of vascular channels inhibits spread of tumor and alters the microenvironment of the tumor bed to the point where viability of the cancer is compromised.

4. Destruction of lymph-node metastases.

5. In some manner enhances the capacity of the host tissue to resist the further extension of the tumor.

6. Usually reduces the size of the uterus, making hysterectomy easier.

7. With vaginal irradiation the possibility of spread in this direction is essentially nullified.

Vaginal Tumors

1. Almost all malignancies of the vagina are extensions of or spread from primaries in the cervix or corpus of the uterus.

2. Primary tumors are uncommon, and most are squamous in type. Rarely adenocarcinomas, sarcomas, or embryonal derivative tumors are encountered.

3. Lesions that are small and well circumscribed are usually treated by intracavitary or interstitial radium. If there is evidence of more extensive tumor involvement, megavoltage irradiation should be added.

4. The sequence of histopathologic effects is similar in most respects to that of like squamous epithelia with the added hazard of injury to the adjacent rectum or bladder.

REFERENCES

Buchler, D. A., et al., 1971, Radiation Reactions in Cervical Cancer Therapy, *Amer. J. Obstet. Gynecol.*, **111**: 745-750.

Cushing, R. M., H. M. Tovell, and L. M. Liegner, 1968, Major Urologic Complications Following Radium and X-Ray Therapy for Carcinoma of the Cervix, *Amer. J. Obstet. Gynecol.*, **101**: 750-755.

Dickson, R. J., 1969, The Late Results of Radium Treatment for Benign Uterine Haemorrhage, *Brit. J. Radiol.*, **42**: 582-594.

Graham, J. B., 1965, Vaginal Fistulas Following Radiotherapy, *Surg. Gynecol. Obstet.*, **120**: 1019-1030.

Gray, L. A., G. L. Peterson, and M. L. Barnes, 1964, Combined Irradiation and Surgical Therapy for Carcinoma of the Cervix

Uteri, in Proceedings of the Fifth National Cancer Conference, Philadelphia, Pa., pp. 229-239.

Kline, J. C., A. E. Schultz, H. Vermund, and B. M. Peckham, 1969, High-Dose Radiotherapy for Carcinoma of the Cervix, *Amer. J. Obstet. Gynecol.,* 104: 479-484.

Peckham, B. M., et al., 1969, Radiation Dosage and Complications in Cervical Cancer Therapy, *Amer. J. Obstet. Gynecol.,* 104: 485-494.

Quan, S. Q., 1968, Factitial Proctitis Due to Irradiation for Cancer of the Cervix Uteri, *Surg. Gynecol. Obstet.,* 126: 70-74.

Ruthledge, F., 1967, Cancer of the Vagina, *Amer. J. Obstet. Gynecol.,* 97: 635-655.

Schier, J. A., R. E. Symmonds, and D. C. Dahlin, 1964, Clinicopathologic Aspects of Actinic Enteritis, *Surg. Gynecol. Obstet.,* 119: 1019-1025.

Sherman, A. I., 1961, A Study of Radiation Failures and the Role of Radioresistance in the Treatment of Cancer of the Cervix, *Amer. J. Roentgenol., Radium Ther. Nucl. Med.,* 85: 466.

Sherman, L. F., K. A. Prem, and N. M. Mensheha, 1971, Factitial Proctitis: A Restudy at the University of Minnesota, *Dis. Colon Rectum,* 14: 281-285.

Strockbine, M. F., J. E. Hancock, and G. H. Fletcher, 1970, Complications in 831 Patients with Squamous Cell Carcinoma of the Intact Uterine Cervix Treated with 3000 Rads or More Whole Pelvis Irradiation, *Amer. J. Roentgenol., Radium Ther. Nucl. Med.,* 108: 293-304.

Thomas, W. O., Jr., H. H. Harris, and J. A. Enden, 1969, Postirradiation Malignant Neoplasms of the Uterine Fundus, *Amer. J. Obstet. Gynecol.,* 104: 209-219.

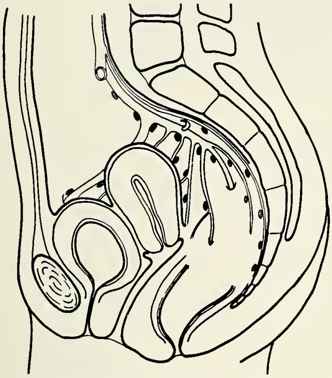


Fig. 11.1 Anatomical relations of pelvic viscera. In this lateral midsagittal diagram of the pelvis, the close proximity of the anterior rectal and posterior urinary bladder walls to the vaginal and endometrial cavities is to be especially noted. The easy accessibility of uterine carcinomas to intracavitary radiotherapy is partially offset by the potential risk to the rectal and bladder mucosae. The relatively remote location of some of the lymph-node groups puts them well beyond the effective range of this form of radiotherapy and necessitates the use of adjunctive remote whole pelvis irradiation to control possible nodal spread.

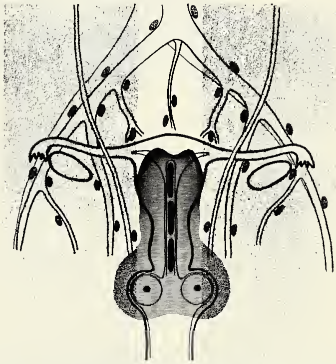


Fig. 11.2 Combined intracavitary and external irradiation of the uterus. This anteroposterior diagram of the uterus and vaginal vault with radium capsules encased in an applicator in position is a graphic representation of the fields of irradiation in combined intracavitary and external therapy. The heavily shaded area is an approximation of the effective range of the intrauterine and vaginal radium, and the stippled areas depict split-field external irradiation to encompass the parametria and lymph-node groups. Appropriate alignment of the opposing portals provides for the inclusion of all node-bearing areas within the range of effective irradiation.

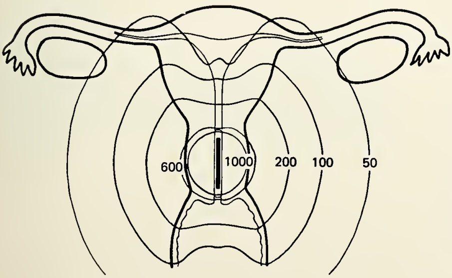
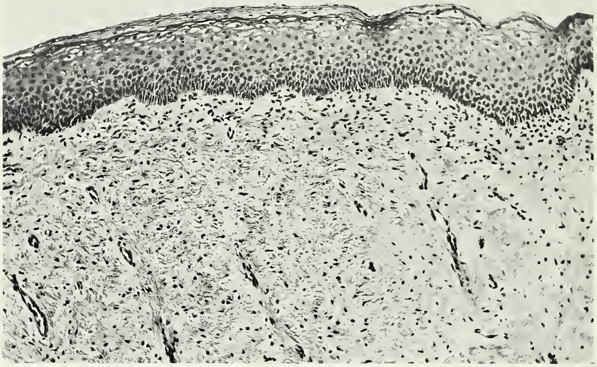


Fig. 11.3 Radium-capsule dose attenuation. This is a graphic representation of the rapid decrease of dose level with distance from a single intrauterine capsule. The dose at the capsule–tissue interface is very high and produces a narrow zone of intense tissue destruction. The effective cancerocidal range of the radiation, however, is only 3.0 cm from the midline when standard sources and times of exposure are used.



(a)

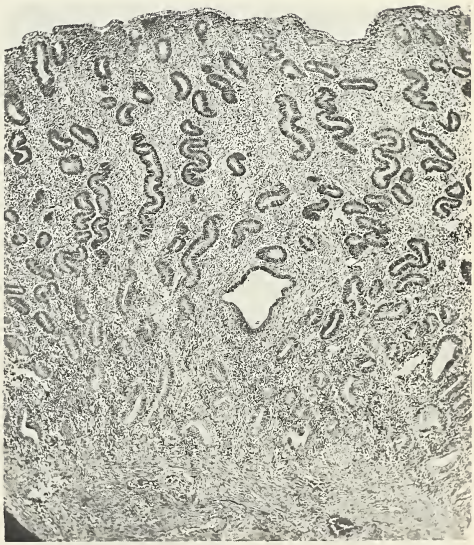
Fig. 11.4 Normal uterine histology. (a) Portio vaginalis of uterine cervix is lined with stratified squamous epithelium resting upon a dense connective-tissue stroma.

(b)

(b) The cervix contains an abundance of noncyclic, mucin-producing, branching glands which open directly to the mucosal surface. These glands are frequently cystically dilated and filled with mucin.

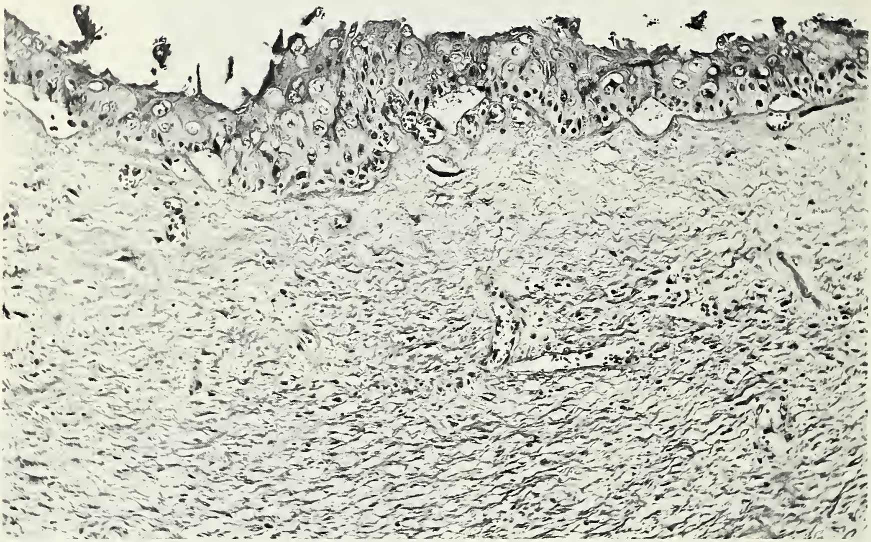
(c)

(c) The transition between the stratified squamous epithelium of the portio vaginalis and the columnar epithelium characteristic of the cervical canal is often abrupt.



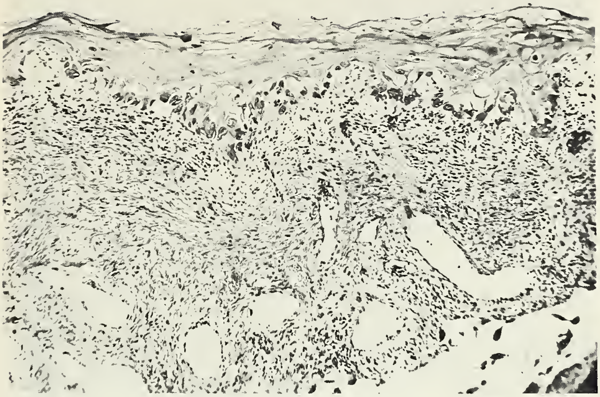
(d)

(d) The endometrial mucosa consists of abundant tubular glands which show some branching in the zone adjacent to the myometrium. These glands are separated by a loose mesenchymal-like stroma. The composition of the endometrium is controlled by the cyclic hormonal influences of the ovaries.



(a)

Fig. 11.5 Early epithelial response to irradiation. (a) The early response of the cervical epithelium results in degenerative changes in the proliferative basal layer. Some of these cells disintegrate rapidly, whereas most exhibit intracellular and extracellular vacuolation, variable swelling of nucleus and cytoplasm, loss of mitotic capability, pyknosis, and karyorrhexis. Pleomorphic cells may be caused by the direct action of the radiation, but most are mitosis-connected cell abnormalities produced when a damaged cell attempts division.



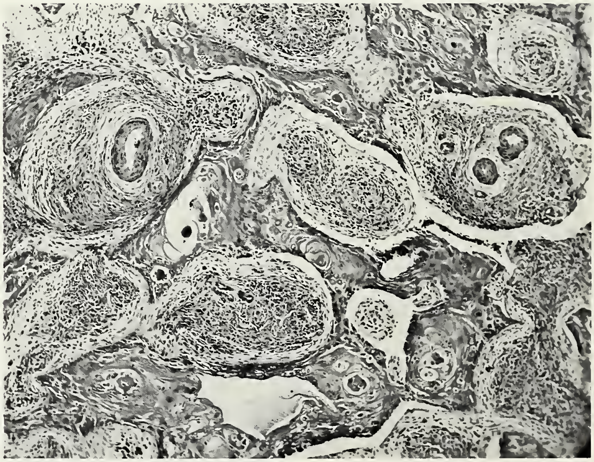
(b)

(b) Because there is no immediate epithelial-cell replenishment, the thickness of the epithelium steadily diminishes. Cells that remain usually undergo premature senile changes and may be retained in situ longer than usual. Cell detail, especially nuclear definition, becomes less evident. Loss of cell cohesion and cell polarity in the basal and parabasal layers is conspicuous. Intercellular vesicles form which may coalesce to produce large bullae that lift the damaged epithelium away from the underlying stroma.

(c) When the therapy has been completed, the stem cells and residual primitive epithelial cells begin the reconstitution of the epithelium. Cell proliferation at the basal zone becomes pronounced, and these rapidly regenerating cells soon force the residual radiation-damaged cells to the periphery where they slough. The completeness of this recovery and the speed with which it is accomplished depend on the viability of the precursor cells, the suitability of the microenvironment, and the absence of intercurrent stress in the form of trauma, infection, or tumor regrowth. In this section the effective destruction of the deep tumor masses is evident.

(c)

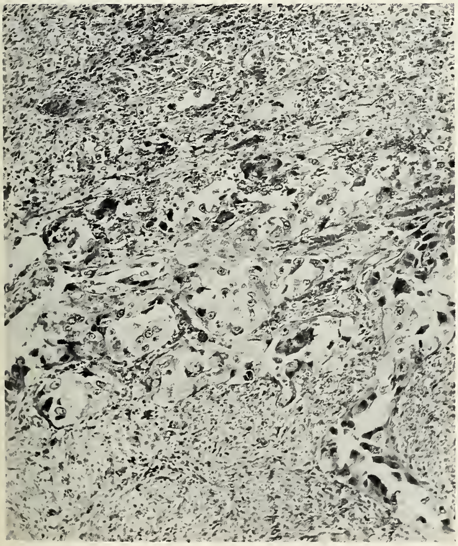
Fig. 11.6 Radiation effect on cervical squamous carcinoma. (a) This section shows a poorly differentiated deeply infiltrating squamous carcinoma with only a few foci of lymphocyte-laden stroma.



(**b**) Following external irradiation there is a change in the morphologic character of the tumor. It now appears to be of a more differentiated keratin-producing type. Almost all these malignant cells are undergoing degeneration with relatively few questionable viable cells at the periphery of the masses. The stroma is now more prominent, and some of the vessels are thick walled.

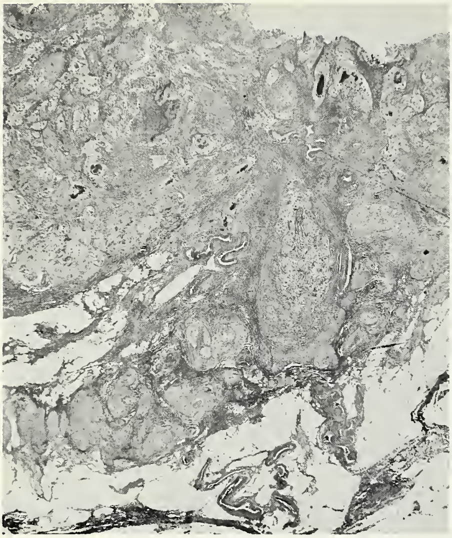
Fig. 11.7 Radiation effect on endometrial carcinoma. (a) Pretherapy biopsy of endometrial carcinoma shows "back to back" elongate glands lined with moderately pleomorphic low columnar to cuboidal cells. Interstitial stroma is almost nonexistent.

(a)



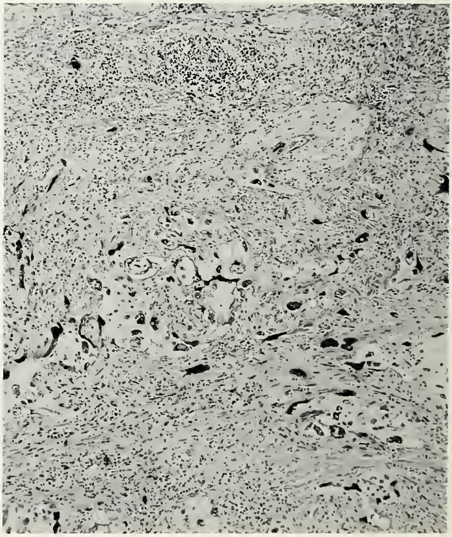
(**b**) The tumor cells following irradiation display marked swelling and pleomorphism. Many cells have lost much of the structural detail, evidencing their relative sensitivity to the radiotherapy.

(b)



(a)

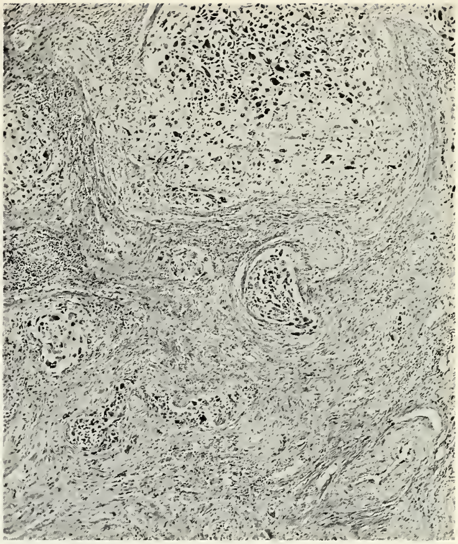
Fig. 11.8 Radium-dose attenuation in a squamous carcinoma. (a) This is a very-low-power photomicrograph showing the complete penetration of a poorly differentiated carcinoma of the cervix from the canal through to the parametrium. Therapy has included both intracavitary radium and total pelvis irradiation from a cobalt source.



(b)

(**b**) Immediately beneath the denuded, ulcerated mucosa the tumor cells are markedly degenerative. There is a severe inflammatory infiltrate.

(c) Deep in the cervical wall the attenuation of the intracavitary-source radiation becomes apparent in the increasing proportion of apparently viable tumor cells. Many of the malignant cells, however, have been destroyed by the radiation. In this zone it is often difficult to assess the proliferative capabilities of the residual cells.



(c)

(d) In the parametrial area it is evident that the cancerocidal potential of the radium has been appreciably diminished with large masses of proliferating tumor cells. Some of the nearby tumor, however, shows degeneration.

(d)

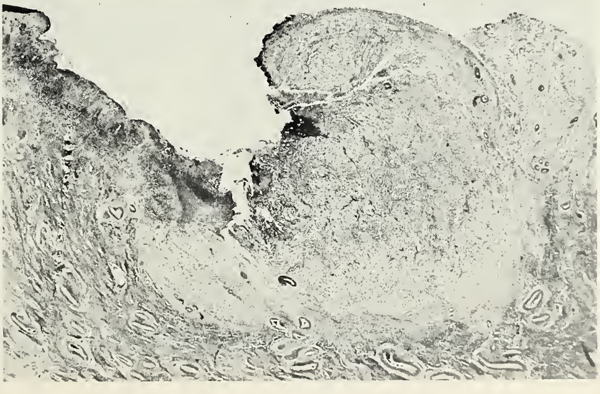
(a)

Fig. 11.9 Delayed response to intracavitary radium. (a) Intracavitary radium is an effective means of controlling superficial carcinomas of the uterus. The physical structure of the capsules and the configurations of the isodose patterns impose some limitations with regard to the containment of the tumor. The intense radiation emanating from the capsules produces a blanched appearance to the superficial mucosa. Note, however, that in most uteri there are deep folds in the endometrial surface which may place distal glands beyond the range of the very high interface dose.

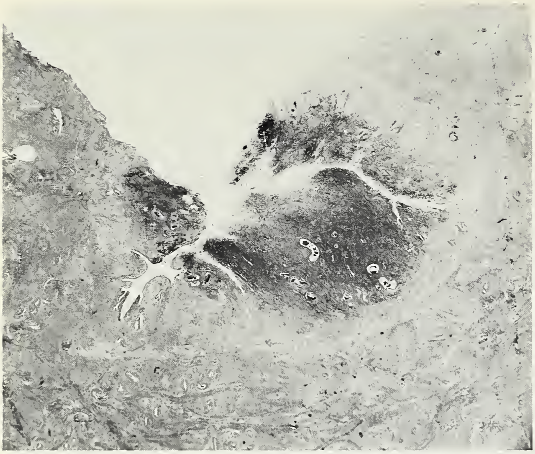
(**b**) This high-power field illustrates the falloff in intensity of the radiation from the capsule "point source." Those epithelial cells closest to the capsule demonstrate bizarre pleomorphism, and the subjacent stroma is dense and hypocellular. As the deeper reaches of the glands are approached, evidence of radiation-related cell injury becomes less manifest. Cells most distant are essentially normal in appearance as is the contiguous stroma.

(**c**) Although superficial portions of the tumor are destroyed, very often there is much more extensive invasion than was evident by preoperative evaluation. This section shows that the majority of the cancer is beyond the highly destructive range of the radium unless the tumor is especially radioresponsive.

(b)



(c)



(a)

Fig. 11.10 Radiation necrosis of uterine mucosa. (a) The early reaction to intracavitary radium may be severe and involve the full circumference of the endometrial cavity. This section shows extensive coagulation necrosis with associated hemorrhage.

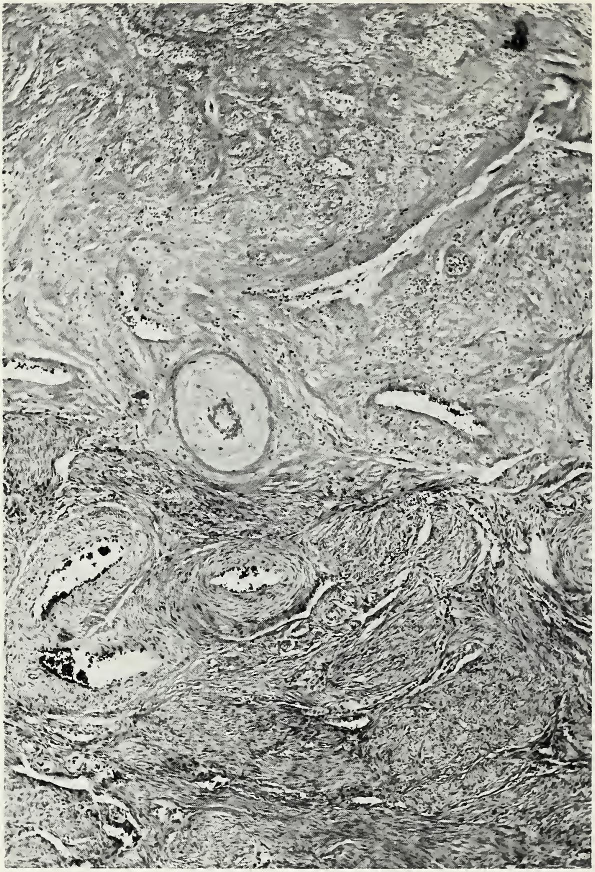
(**b**) As the more acute response begins to resolve, the coagulation necrosis and hyaline degeneration become more apparent. The surface is partially relined with a single layer of low columnar to cuboidal cells. Some of the residual cystic glands contain cell debris and have a lining of atypical epithelial cells.

(b)

(a)

Fig. 11.11 Delayed response to intracavitary radium. (a) This low-power, long-axis section through the corpus of the uterus illustrates the often sharp demarcation between the inner zone of intense hyaline degeneration produced by intracavitary radium and the broad outer mass of essentially normal-appearing myometrium.

(Figure continues on following page.)



(b)

(**b**) This abrupt transition from severe tissue degeneration to myometrium showing minimal vascular and smooth-muscle changes could only be produced by a sharp reduction of radiation-energy transferral. The affected tissue is undergoing a hyaline degeneration and is distinctly hypocellular in comparison with the underlying myometrium. Vessels show loss of endothelium, smudged intimal thickening, loss of media detail, and a dense acellular adventitia.

Chapter 12
Brain and Spinal Cord

NORMAL STRUCTURE AND FUNCTION

The primary functional activities of the brain and spinal cord are

1. Input. Information reception from peripheral sensors and stimuli.
2. Storage and utilization. "Programming" of information and indexed storage.
3. Output. Recall of data, determination, and transmission to motor organ.

Most of this "computer" operation is carried out within the highly specialized and complex tissues of the brain with the spinal cord serving as the main courier and relay system.

Neuron

The principal functional cell is the neuron. Although present in great abundance in the central nervous system (CNS), it has a small population density in comparison to the other, smaller nerve-tissue cells that provide the necessary structural support and nutrition.

The neuron is a large cell of complex structure and composition. It has a large nucleus, usually with a single large nucleolus. The perikaryon (cytoplasm) contains neurofibrils, Nissl bodies, mitochondria, Golgi apparatus, and various inclusions. The neuron processes consist of several short dendrites emanating from the main cell bòdy and the single axon, which may be very long with its terminus in some distant part of the body.

Neuroglia

The neuroglia (glia) are the supportive cells for the neurons and include astrocytes, oligodendrocytes, and microglia. They form a dense mesh of plasmatic processes within which are the neurons separated from each other except for their required synapses. The neuroglia seem to have an active role in maintaining the finely balanced metabolism of the neurons. Usually they play a role in the response of the CNS to injury.

Ependyma

The ependyma, of epithelial nature, is often classified with the neuroglia even though of different embryonic derivation. It consists of low cuboidal cells that line the ventricles and ducts of the brain and spinal cord.

Meninges

The meninges are the connective-tissue membranes (dura mater, arachnoid, and pia mater) that encase and protect the brain and spinal cord. Through these membranes course the main vascular radicles with branches that penetrate deep into the substance of the brain and cord invaginating the pia mater all the way to the microvascular level and forming in this manner the perivascular Virchow–Robin space.

CLINICAL SYNDROME—BRAIN

In most cases variable amounts of parenchymal damage already exist at the time radiotherapy is begun as a result of the presence of neoplasm and frequently some form of surgical intervention, either diagnostic or attempted decompression and/or tumor extirpation.

The postirradiation clinical response under these circumstances must be evaluated in the light of the following:

1. During its growth within the brain parenchyma, the tumor has been responsible for the development of a complex of progressive neurological signs and symptoms.
2. Diagnostic or therapeutic surgery will have been performed in most cases and will modify to some degree the clinical manifestations.
3. The response of the neoplasia (with the probable added factor of intercurrent surgical trauma) may completely obscure any overt effect that irradiation may produce in relatively normal parenchyma.

Early Response

Nonspecific pretherapy signs and symptoms, such as headache, nausea and vomiting, lethargy, and papilledema, are abruptly amplified.

In addition, certain of the more specific and localizing characteristics of a brain lesion may also be altered by the radiation, i.e., paresis, aphasia, ataxia, convulsive episodes, and specific cranial nerve deficits.

These early clinical changes could quite obviously result from a variety of intercurrent events, such as hemorrhage

within the tumor, vascular compromise in relation to surgery, spontaneous degeneration of tumor tissue, and radiation-induced edema within the invaded parenchyma and its often broad contiguous cuff of reactive brain substance. In this latter regard, experimental evidence suggests that normal brains are able to tolerate radiation doses at the therapeutic level without significant accumulation of edema.

COMMENT. It is really only the close time association with irradiation that suggests the etiological relationship.

TREATMENT. Definitive management of a severe, early posttherapy response is frequently unsatisfactory and hazardous. It is much more important to apply appropriate prophylactic steps to minimize the possibility of an early untoward reaction.

There are at least three approaches to the control of the possible excessive accumulation of parenchymal fluid: (1) assuring the patency of cerebrospinal fluid circulation and drainage, (2) providing a bone flap to absorb abrupt brain swelling, and (3) regulating the administration of the radiation to avoid further insult at the first indication of early difficulty.

Delayed Early Response

The most important clinicopathologic consideration of this phase of the clinical syndrome is to recognize that the greatest degree of radiation effect on tissue has been directed at the tumor and the surrounding zone of modified brain parenchyma. This altered tissue by its varied, atypical, and often richly vascular composition is generally relatively responsive to radiation.

(1) The radiation effect may be exceptionally beneficial with permanent reversion of signs and symptoms toward a more normal state. (2) There may be recurrence of many of the neurological complaints after an initial encouraging remission. (3) Subsequent to radiotherapy there may be several months of a persistent and virtually unchanging neurological deficit with a sudden unexpected increase in the signs and symptoms and perhaps added changes.

In the latter two instances, the "turn for the worse" after a variable period of seeming stabilization becomes an exercise in differential diagnosis and carefully considered patient management.

Contemplation of any further definitive therapy must await a positive tissue diagnosis; there is no acceptable alternative. Experience has indicated that even the risk of a diagnostic craniotomy is preferred to the morbidity associated with a repeated course of radiation therapy. Brain necrosis and degenerative effects from whatever cause can mimic the regrowth of the space occupying tumor.

Certain nontraumatic tests may be helpful but unfortunately are neither infallible nor consistent. The EEG patterns are generally equivocal. Brain scans should theoretically disclose increased concentrations in tumor recurrence; however, prior surgery and radiotherapy or hemorrhage within necrotic tumor can obscure or distort the pattern and render the result inconclusive. These same problems will affect arteriography and ventriculography. An expanding neoplasm is more likely to produce signs and symptoms of increased pressure than will the degenerative changes following irradiation; however, this effect is usually not severe enough to be of definitive diagnostic value.

COMMENT. The obvious question regarding the development of this clinical syndrome is just what can be done for the patient once the diagnosis has been established.

1. If the expanding lesion is a cystic residuum of radionecrosis or a zone of infarction, removal of entrapped fluid or necrotic debris may produce reversal of signs and symptoms.

2. Most important, biopsy can prevent the disastrous reirradiation of a nontumorous area.

3. Presence of recurrent tumor sets the stage for further surgical resection and decompression and possibly additional carefully applied radiation. Neither of these alternatives is likely to provide more than very temporary relief.

Delayed Late Response

The inclusion of this category is arbitrary because the delayed clinical syndrome may extend over a period of many years, and it is only of academic interest to consider early and late stages of the delayed radiation encephalopathy.

It is likely that almost all late manifestations are consequences of progressive vascular sclerosis rather than effects of direct nerve-cell injury. In most instances the very slow development of this condition produces almost undetectable changes in the neurological pattern.

Occasionally, occlusion of a major vessel may result in a sudden stroke-like event, or an area of cystic necrosis may become distended and act as an expanding lesion.

Since there is no recovery as such from the late sequela of irradiation, treatment is entirely supportive, and appropriate measures should be taken to compensate, insofar as possible, for the permanent functional decrement.

CLINICAL SYNDROME—SPINAL CORD

As noted, the general structural and functional characteristics of the brain and spinal cord are similar; therefore the fundamental anatomical and functional response to radiation should be comparable in most respects. The one major difference in radiation effects in these two components of the CNS is the very high proportion of parenchymal neoplasia and surgery in the brains irradiated as opposed to the incidental nature of the spinal cord exposures. Deliberate radiotherapy of the spinal cord for an intrinsic lesion is uncommon and considered appropriate only for the treatment of known radioresponsive neoplasms, most of which spread via the meninges.

Extraordinary technical advances in radiotherapy and vastly improved radiation sources used in conjunction with surgery and/or chemotherapy have prompted more aggressive treatment of neoplasms in the head and neck and deep thoracic viscera.

Appropriate shielding and careful columnation and direction of the radiation beam greatly reduce the hazard to the cervical and thoracic cord; however, the total dose required for effective tumor control may be large, and the potential risk of cord injury increases in proportion to the intensity of the treatment.

Several attempts have been made to categorize the clinical syndromes relating to irradiation of the spinal cord. Most of them are based upon insufficient clinicopathologic correlative data and case numbers of little statistical value.

There are probably three types of radiation myelopathy:

1. The mildest form reflects minimal cord damage and manifests itself as vague, inconsistent, and transient symptoms without any neurological signs detectable by the usual screening tests and examinations. It is very likely that this response goes unrecognized or is attributed to some disease not related to radiation. By description, its incidence cannot be determined; however, it is logical to assume that a significant proportion of patients whose cord areas receive moderate to large doses of radiation will react to the insult in some fashion. This could be classified as an early response since it would generally be associated with the more acute and reversible vascular phenomena.

2. The most common form of radiation-induced myelopathy that has identifiable clinical characteristics and more severe related histopathology is the delayed—up to many months or years—and slowly progressive disease. The insidious onset is often in the form of increasing numbness, loss of pain and/or temperature sense, painful paresthesias, and weakness in one or both lower extremities. "Electric shock-like" pains in the back (Lhermitte's sign) may be an early complaint.

The milder forms of this type of myelopathy may occasionally show some degree of stabilization and rarely some eventual slight reversion of the neurological decrement. In general, however, the changes are relentlessly progressive with subsequent involvement of the trunk and upper extremities (especially in cervical-cord irradiation) and total loss of bladder and bowel control. It has been reported that there is initially relatively rapid development of this syndrome followed by slower progression. The prognosis is dismal, the average survival after onset of symptoms being about 10 months.

3. It has been postulated that there may be a third type of myelopathy although this is not supported by histopathology. Possibly during the development of the vascular sclerosis, which is the underlying mechanism of the delayed myelopathies, there may be a sudden occlusion of a major nutrient artery by thrombosis or mural hemorrhage. The result would be a possible transection of the cord as in infarct and a clinical state of abrupt paraplegia and possibly respiratory arrest.

COMMENT. Because of the frequently extended delay in the onset of symptoms, some of these cases may become problems in differential diagnosis.

1. Extramedullary metastases from the primary neoplasm should be detectable by myelography. Primary tumors of the head, neck, and thorax rarely metastasize to the cord meninges.

2. Intramedullary metastases or primary cord tumor. These are even more rare and should be last on the list of possible etiologies.

3. In this same range of remote possibility is the so-called carcinomatous myelopathy, which is not associated with head and neck malignancies.

4. Focal vascular occlusion not directly related to irradiation is unlikely unless there has been extensive scarring of the contiguous tissues, which eventually encroach upon the nutrient vessels.

5. Collapse of a vertebral body or a herniated nucleus pulposus would produce an acutely developing syndrome and usually be detectable by myelography and spinal-fluid dynamics.

6. Primary degenerative cord diseases have much more protracted clinical courses marked by remissions and a great diversity of neurological manifestations.

RADIATION HISTOPATHOLOGY (RADIATION ENCEPHALOPATHY AND RADIATION MYELOPATHY)

To comprehend the variance of the clinical impact of radiation effects in the brain and spinal cord, one should reconsider certain aspects of the anatomy and function of these two components.

The brain is a relatively large organ, which, like a highly complex electronic computer and control center, spatially orients specific functional responsibilities to circumscribed parenchymal foci or action/reaction stations. Most such response centers are paired hemispherically to correlate with their respective contralateral spheres of influence or areas of responsibility. Many such brain loci, although a part of the normal sensorium of the individual, are not, in the strict sense of the word, vital to the critical functional programming of the brain and have been inappropriately referred to as "silent" areas.

From this brief comment, therefore, it is apparent that most focal parenchymal damage may alter the functional states of specific, well-defined response centers, and the clinical manifestations will assist in identifying the site of the lesion. Injury in a predominantly silent area, however, may evoke minimal nonspecific clinical reactions.

The spinal cord is the elongate component of the CNS. It could be likened to the major conduit of the master control center which is responsible for the transmittal of input and output impulses connecting the action/reaction stations in the brain with their respective areas of responsibility and with the rapid mediation and relay of reflex responses. The cross section of the cord consists almost entirely of communicating tracts, and there are no silent areas. Injury to the cord, even though of small circumscribed nature, is capable of producing dramatic neurological deficits.

COMMENT. The nervous tissue has always been considered to be relatively unresponsive to the actions of ionizing radiation. This assumption has been a major factor in the formulation of energetic radiotherapy for neoplasms involving the brain and spinal cord directly or for lesions contiguous with, or in the vicinity of, these structures. Experience has shown, however, that large doses cannot be administered with impunity, and not infrequently a heavy price will be extracted in physical debility and patient discomfort for whatever effected control of the tumor might be achieved.

In defense of aggressive treatment policies, especially as directed at primary and secondary brain tumors, is the almost hopeless prognostic situation of so many of the patients submitted for treatment and the capacity of forceful irradiation to frequently greatly diminish the distressing symptoms. In most instances, radiation therapy represents the only feasible means of possible cancer control.

General Considerations

The effects of radiation on the CNS are so shrouded in contention that they are not conducive to an outline consideration; therefore, a more narrative description has been applied.

For many decades the nervous tissue has been considered to be relatively unresponsive to the actions of ionizing radiation. For this reason, large doses have in the past been administered with the assumption that this intensive radiation therapy could be employed with relative impunity. It soon became obvious, however, that such was not to be the case as indisputable evidence of late-developing necrosis of the irradiated brain and spinal cord areas began to appear with increasing frequency in the literature. Two theories of pathogenesis of this delayed degenerative effect prompted a surge of investigations each designed to prove or disprove the nature of the damage. The greatest volume of recent research tends to support the vascular-compromise theory although there are still strong proponents of the direct nervous-tissue involvement with prolonged response time. It is indeed probable that both factors may be responsible for the late radiation effects.

Protracted response times following CNS irradiation have been recorded for a variety of animal species and emphasize the importance of this time factor in the appearance and the interpretation of radiation effect. Excellent investigations have characterized the changes of acute irradiation in a variety of animals; however, this has been accomplished only by employing unusually high doses given as a single exposure. Except with extremes of localized dose (usually greater than 10,000 rads), this acute response resembles in many respects an inflammatory reaction and is pale by comparison with the severe delayed damage.

COMMENT. Several investigators have established clear relationships between period of system development and degree of sensitivity to radiation. In general, prenatal and neonatal animals are markedly susceptible to the actions of ionizing radiation in comparison to those which are not exposed until several days or weeks postnatal. Although a pronounced developmental and adaptive process occurs during the paranatal period which would diminish the tolerance of the tissue to the trauma of irradiation (or any other stress for that matter), the underlying mechanisms through which these changes develop are as yet unclear. The undeniable hazard of exposing the developing fetus and especially the developing CNS to any radiation deters the employment of this mode of therapy in pregnancy unless abortion is assured.

Likewise radiotherapy to the head region of the infant must be carried out with great caution and circumspection.

Vascular Changes

As is true in all tissues, there is a significant vascular component to both the acute and delayed phases of CNS injury. Although the relative importance of this vascular effect has not been accurately assessed, most investigators are inclined to make it a primary determinant in the pathogenesis.

ACUTE EFFECTS. 1. Swelling of endothelial cells occurs with an increase in the nuclear staining. The swelling may be transient and either reversible or progressive to vessel barrier compromise.

2. There is increased permeability even in those microvessels whose structural integrity seems visually to be preserved.

3. As a result, there is perivascular accumulation of erythrocytes, leukocytes and fluid.

4. As in other tissues, the microvasculature displays the greatest effect in acute radiation injury. This would seem to account for the presence of focal minute hemorrhages in exposed brain and the conspicuous absence of any large hemorrhage (i.e., greater than a perivascular "cuff" hemorrhage).

5. This microcirculatory compromise may encompass a large enough volume of tissue that some degree of gross tissue edema may develop. This is uncommon except in the presence of a large tumor mass.

DELAYED EFFECTS. 1. Necrosis and rupture of the walls of arterioles may be associated with an infiltration of inflammatory cells, usually lymphocytes, monocytes, and macrophages.

2. There is fibrinoid or hyalinoid degeneration of vessel walls, with subsequent fibrosis and luminal constriction.

3. Thromboses may supervene to complete the occlusion.

4. It is probable that these vessel changes are initially segmental and that a single histologic section may not reflect the severity of the injury to the overall vascular component. Serial slide preparations will usually disclose random thickening of the vessel walls.

Nerve Parenchyma Changes

The proponents of the direct-cell-injury theory are hard-pressed to proffer clearly delineated nervous-tissue changes in the absence of vascular change except in instances of very-high-dose focal exposure.

One of the major arguments propounded by those investigators who advocate a direct effect upon the tissue of the CNS is based upon response times. It is their viewpoint, and with some justification, that the majority of injuries sustained by the nerve cells produce no early morphologic change and that this postirradiation latent period for overt structural manifestations exceeds the relatively short response time of the vessels. This does not, however, preclude the possibility of early development of functional deficits of micromagnitude that current instruments lack the sophistication to detect. These investigators further hypothesize that the protracted reaction period allows for the restitution or repair of many sublethal structural and functional defects in the primary nerve cells.

1. As already observed, the developing nerve cell (structural and functional) is responsive to the action of radiation. This sensitivity, however, apparently decreases dramatically in the early postnatal period.

2. The granule cells of the cerebellum respond promptly to acute irradiation by becoming pyknotic. This process may be transient and reversible, or random granule cell degeneration with diminished population density may occur. This granule cell is the only cell of the nerve-tissue proper which displays distinctive and consistent alterations without significant concomitant microvascular injury.

3. Early morphologic changes have been reported in Purkinje cells and in neurons especially in specific loci. These observations are inconsistent and lack clear definition.

4. Myelin degeneration is a frequent occurrence in areas of irradiation. The pathogenesis is obscure, although there is a probable relationship to degenerative changes in the conjunctive oligodendrocytes.

5. With regard to the effect of radiation on the glial cells, there is once again a distinct lack of unanimity of opinion among the principal investigators. Some imply that these cells are relatively resistant to the action of high-energy radiation, whereas others report various degenerative changes in the astrocytes and oligodendrocytes even at modest dose levels.

6. The meninges respond early to irradiation even in the relatively low dose range of several hundred roentgens. The process is that of an inflammatory-type reaction that infiltrates granulocytes and later mononuclear cells.

7. These widely divergent views with regard to the overall pathogenesis of CNS irradiation must be carefully considered in the final evaluation of any case of early or delayed damage in an irradiated brain or spinal cord. It must be recognized that there remains a mountain of experimentation to be completed before the basic mechanics of this response will be understood.

COMMENT. The divergence of experimental results may be entirely inadvertent and stem from variation in animal model species, age and sex groupings, individual animal susceptibility, characteristics of the radiations as well as modes of application, environmental states, and procedural methods. To this is added the subjective difference in interpretation of results, and it is small wonder that some of the camps are widely separated.

Sequential Response Pattern

From all this confusion, however, certain features develop which are observed with enough consistency to be classified as characteristic of the response of the CNS to therapeutic irradiation.

EARLY PHASE. 1. Microvascular injury (may be transient) with possible focal relative ischemia of dependent parenchyma.

2. Extravasation of erythrocytes, leukocytes, and variable amounts of plasmatic fluid.

3. An inflammatory type response in the meninges.

4. Variable random pyknosis of cerebellar granule cells (may be transient).

LATE PHASE. 1. Apparent dominance of vascular damage—progressive sclerosis and thrombosis.

2. Associated areas of demyelination, depletion of glia and neurons, and necrosis. The white matter seems to be more severely affected than the gray matter. There are irregular but relatively well-defined areas of demyelination and some nerve-cell degeneration that roughly coincide with the distribution of constricted vessels entering the CNS substance.

3. As a necrotic lesion develops, the less severely damaged tissues at the periphery will respond with mobilization of phagocytic cells, glial proliferation, and neovascularization.

4. Fibrosis of the overlying meninges and extension of fibrosis into the Virchow–Robin space.

5. The loss of integrity of the vascular barrier is a consistent finding and is marked by fibrinoid degeneration of the vessel wall, deposition of protein-rich substance in the subendothelium and media, and the extravasation of erythrocytes. As in all areas where this process develops, it would seem probable that this would be responsible for a severe compromise of metabolite interchange.

6. The possible activation of a latent neurotropic virus might explain the differences of experimental results among animal species and in different laboratory environments. It is also known that such laboratory animals as the rat, rabbit, dog, and even monkey may spontaneously develop a variety of neurologic diseases that could invalidate the experimental results.

COMMENT. 1. One reason for the difficulty in establishing the pathogenesis of radiation effects in the CNS is the heterogeneous composition of this tissue and the lack of techniques sophisticated enough for determining the functional and structural states of the diverse cell types.

Of all the cell populations represented, only two are moderately sensitive to therapeutic doses of radiation—the endothelial cell and the granule cell of the cerebellum. Most of the other cells, including the connective-tissue elements of the meninges and the glial cells, are relatively unresponsive and are conditionally proliferative. The principal parenchymal cell, the neuron, is nonproliferative and by current criteria must be considered resistant to radiation.

2. Functional stability in the neuron depends upon a very delicately balanced microenvironment. It is logical to assume that any degree of compromise of the microcirculation, even though it be transient, could have a significant effect upon the intraneuronal processes.

The blood–brain barrier has been a topic of contention for many years, and the exact nature of this selective passage between the circulating elements and the parenchyma has not been fully established. The mechanics of this barrier are unknown, and the anatomical site, if indeed it can be identified at all, can only be surmised. The two possible loci are the endothelium and the confluent attachments of the neuroglial cells which are contiguous with the perivascular boundary. Because the functional integrity of this barrier controls the composition of the diffusate through the vessel wall and into the parenchyma, the effect of radiation upon this critical structure may be of great concern.

PROBLEMS IN THERAPY

Of primary concern is the inherent inability of the neurons to regenerate. The neoplasm that has prompted the consideration of therapeutic irradiation has already caused some degree of neurologic damage by its space-occupying and invasive propensities. The application of radiation to this area may either diminish the volume of the tumor and reestablish some of the neurologic pathways which are salvageable or increase the deficit that already exists. This latter effect may prove to be a transient response owing to the already described early microcirculatory compromise or the result of an indirect reaction mediated by the toxic products of large numbers of degenerating tumor cells.

The location of the lesion to be irradiated is also critical. It has been noted that some areas of the brain appear to be more susceptible, i.e., the white matter and brain stem. What is more important, however, is the criticality of the nerve control that is exercised by that particular region of the brain which is involved. There is much less risk insofar as treatment (surgical and/or radiation) is concerned if the lesion is located in a so-called silent area.

Preexistent or concomitant disease states, such as arteriosclerosis and encephalopathies, from whatever cause may greatly enhance the danger of energetic therapy. The treatment of such individuals must be undertaken with great caution and increased surveillance.

The age of the patient predicates the total dose and the nature of the fractionation. The younger the individual, the more sensitive the nerve tissue to radiation and the greater the care that must be employed in treatment.

REFERENCES

Atkins, H. L., and P. Tretter, 1966, Time–Dose Considerations in Radiation Myelopathy, *Acta Radiol.*, 5: 79.

Berg, N. O., and M. Lindgren, 1958, Time–Dose Relationship and Morphology of Delayed Radiation Lesions of the Brain in Rabbits, *Acta Radiol.*, 167: 1-118.

Bouchard, J., 1966, Radiation Therapy of Tumors and Diseases of the Nervous System, Lea & Febiger, Philadelphia.

Brownson, R. H., W. M. Shanklin, and D. B. Suter, 1964, A Study in Chronic Brain Radionecrosis, *J. Neuropathol. Exp. Neurol.*, 23: 660.

Courville, C. B., and R. O. Myers, 1958, The Process of Demyelination in the Central Nervous System, *J. Neuropathol. Exp. Neurol.*, 17: 158-181.

Crompton, M. R., and D. C. Layton, 1961, Delayed Radionecrosis of the Brain Following Therapeutic X-Radiation of the Pituitary, *Brain*, 84: 85-101.

Dugger, G. S., J. G. Stratford, and J. Bouchard, 1954, Necrosis of the Brain Following Roentgen Irradiation, *Amer. J. Roentgenol., Radium Ther. Nucl. Med.*, 72: 953.

Dynes, J. B., and M. I. Smedal, 1960, Radiation Myelitis, *Amer. J. Roentgenol., Radium Ther. Nucl. Med.*, 83: 78-87.

Haymaker, W., 1969, Effects of Ionizing Radiation on Nervous Tissue, in *Structure and Function of the Nervous System*, Vol. 3, Chap. 10, G. H. Bourne (Ed.), Academic Press, Inc., New York.

——, et al., 1968, Delayed Radiation Effects in the Brains of Monkeys Exposed to X- and Gamma Rays, *J. Neuropathol. Exp. Neurol.*, 27: 50-79.

——, et al., 1958, The Effects of Barium 140–Lanthanum 140 (Gamma) Radiation on the Central Nervous System and Pituitary Gland of Macaque Monkeys, *J. Neuropathol. Exp. Neurol.*, 17: 12-57.

Lampert, P. W., and R. L. Davis, 1964, Delayed Effects of Radiation on the Human Central Nervous System, *Neurology*, 14: 912.

——, et al., 1959, Disseminated Demyelination of the Brain Following Co-60 (Gamma) Radiation, *AMA Arch. Pathol.*, 68: 322-330.

Locksmith, J. P., and W. E. Powers, 1968, Permanent Radiation Myelopathy, *Amer. J. Roentgenol., Radium Ther. Nucl. Med.*, 102: 916.

Maier, J. G., et al., 1969, Radiation Myelitis of the Dorsolumbar Spinal Cord, *Radiology*, 93: 153.

Pallis, C. A., et al., 1961, Radiation Myelopathy, *Brain*, 84: 460-479.

Pennybacker, J., and D. S. Russell, 1948, Necrosis of the Brain Due to Radiation Therapy: Clinical and Pathological Observations, *J. Neurol., Neurosurg. Psychiat.*, 11: 183.

Reagan, T. J., J. E. Thomas, and M. Y. Colby, Jr., 1968, Chronic Progressive Radiation Myelopathy: Its Clinical Aspects and Differential Diagnosis, *J. Amer. Med. Ass.*, 203: 106.

Scholz, W., and Y. K. Hsu, 1938, Late Damage from Roentgen Irradiation of the Human Brain, *Arch. Neurol. Psychiat.*, 40: 928-936.

Vaeth, J. M., 1965, Radiation-Induced Myelitis, in *Progress in Radiation Therapy*, Vol. 3, F. Buschke (Ed.), Grune & Stratton, Inc., New York.

Wachowski, T. J., and H. Chenault, 1945, Degenerative Effects of Large Doses of Roentgen Rays on the Human Brain, *Radiology*, 45: 227.

Zeman, W., Pathogenesis of Radiolesions in the Mature Central Nervous System, USAEC Report BNL-9345, Brookhaven National Laboratory, 1965.

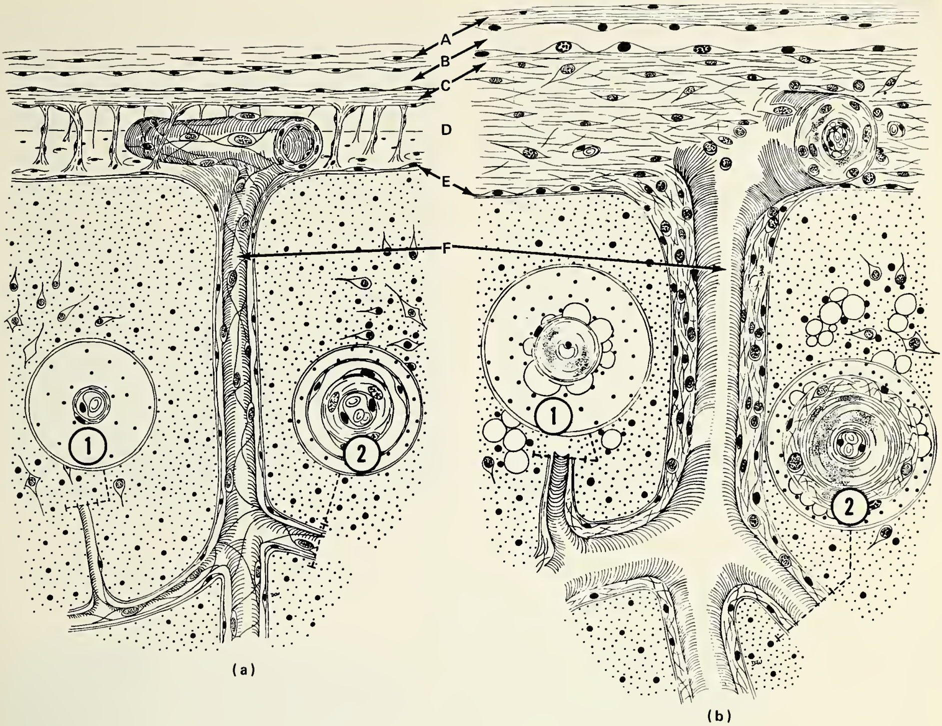
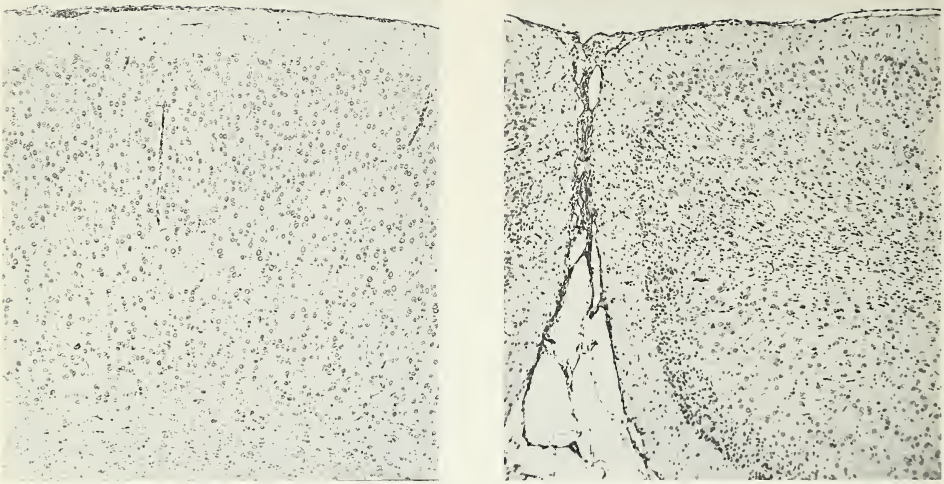


Fig. 12.1 Unirradiated cerebral cortex and delayed radiation encephalopathy. (a) This schematic drawing shows certain of the fundamental structural details of the normal cerebral cortex. (A) The tough dense dura, which adheres to the inner table of the skull. The inner surface is coated by a layer of flattened mesothelial cells and is separated from the leptomeninges by a fluid-containing subdural space (B). The arachnoid (C) is a delicate membrane that encases the brain and connects with the underlying pia mater by delicate connective-tissue strands. The subarachnoid space (D) is inconspicuous except at the sulci and fissures. The pia mater (E) adheres to the brain surface and invests the blood vessels. Its surface and the inner and outer surfaces of the arachnoid are covered by a monolayer of attenuated mesenchymal cells. As the branches of the pial vessels penetrate the brain parenchyma (F), they invaginate the connective-tissue elements of the pia membrane to form the perivascular Virchow–Robin spaces (seen in cross section in insert 2), which extend into the tissue to the arteriolar level. Insert 1 shows the close contiguity of the microvascular structures to the brain parenchyma.

(b) The delayed radiation encephalopathies are primarily in response to progressive vascular sclerosis. All ramifications of the pial vessels can demonstrate the effects of irradiation. In most instances there will be some degree of endothelial proliferation and plasmatic transudation in the subendothelial and medial layers. Of even greater prominence may be the connective-tissue proliferation in the Virchow–Robin space which further compresses the vessel lumens and increases the barrier between the circulating blood and the parenchyma. Associated with this perivascular fibrosis may be an obliteration of the arachnoid-pia space by connective-tissue proliferation. One consequence of this developing circulatory compromise is a relative ischemia in the dependent parenchyma, which reacts first by demyelination, which then gives way to a progressive focal necrosis.



(a) (b)

Fig. 12.2 **High-dose monoenergetic proton-beam irradiation of rat cerebrum.** **(a)** The circumstances of standard radiotherapy, even total doses of several thousand rads, seldom elicit any significant or consistent early histopathology in normal cerebral cortex. Microvascular injury undoubtedly occurs but may be transient, and the secondary changes in nerve tissue are generally slow to evolve and sporadic in distribution. Some insight into prompt brain damage from radiation may be achieved by evaluating the histologic changes produced by very-high-dose, unidirectional and monoenergetic beams that have a finite penetrability in tissue. This photomicrograph is from the unirradiated hemisphere of rat brain and shows clearly the thin meninges, the relatively hypocellular molecular layer, and the underlying granular and pyramidal layers.

(b) The proton beam was directed downward into the cerebrum with a very limited ability to penetrate. The abrupt deceleration of this corpuscular irradiation produced a narrow zone of intense ionization and energy transfer which is referred to as Bragg's peak. The sharp demarcation of maximum penetration is readily observed in this section of cerebrum irradiated a few days previously. In the Bragg-peak zone, the nerve cells are degenerative with severe nuclear pyknosis. The degree of parenchymal damage diminishes toward the cortical surface.

(c) This high-power photomicrograph emphasizes the linearity of the Bragg-peak effect and shows the shrinkage of the nerve-cell nuclei, pyknosis, and some glial response. Note the apparent separation of the brain parenchyma from the capillaries, by plasmatic transudate.

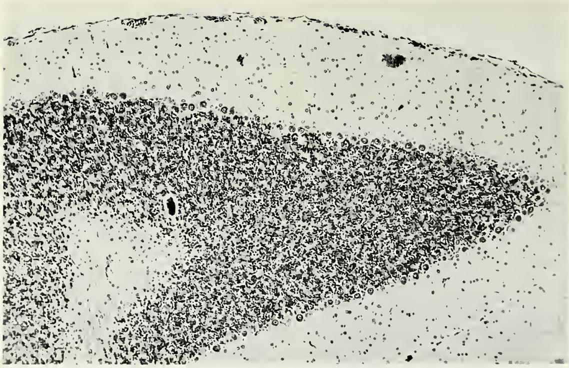
(c)

(d)

(d) The effect of time on the development of a localized area of severe brain damage. An intermediate stage with obvious reduction in the nerve-cell population in the zone of maximum effect. The stroma has a spongy appearance owing to the loss of myelin and the dropping out of cells. There is slight glial proliferation at the edges of the degenerative area. The microvasculature is becoming more readily identified because of thickened walls. A few microhemorrhages are present. There is early edema and fibrosis of the overlying meninges.

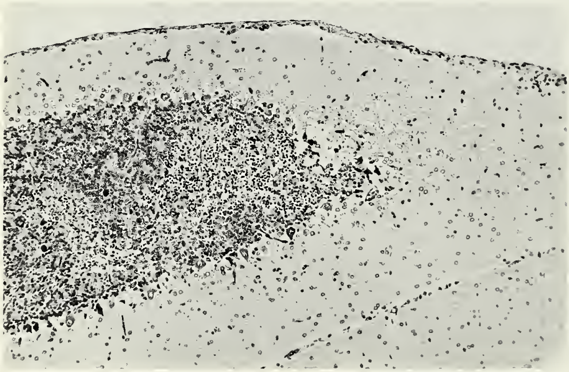
(e)

(e) The effect of time on the development of a localized area of severe brain damage. The appearance at several weeks postirradiation. Almost the entire peripheral cortex is necrotic with only a few tags of glial tissue. There are small hemorrhages and dilated vascular spaces. A small, sclerotic penetrating artery is seen at the right of the section. Note that there is now some advancement of the degeneration beyond the previous sharp line of demarcation owing to the increasing vascular compromise.



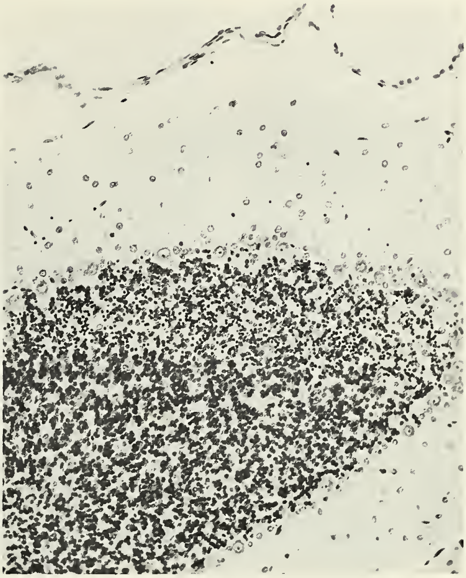
(a)

Fig. 12.3 High-dose monoenergetic proton-beam irradiation of rat cerebellum. (a) The granule cells of the cerebellum are peculiarly responsive to radiation and react promptly by demonstrating nuclear shrinkage and chromatin condensation. This effect may be transient depending upon the magnitude of the dose absorbed. This photomicrograph is from a portion of unirradiated rat cerebellum and clearly shows the histological characteristics. The peripheral molecular layer contains relatively few nerve cells and consists largely of the dendritic processes of Purkinje cells and axons of the granule cells. Some basket cells and other neuroglia are present. At the interface between the molecular and granular layers is the monolayer of large Purkinje cells. The granule layer is densely cellular and encloses a central white matter of afferent and efferent fibers.



(b)

(b) Subsequent to proton beam irradiation, the zone of maximum effect is easily identified by the pyknotic granule cells. In addition, spongy demyelination and focal loss of Purkinje cells occur as well as meningeal fibrosis.

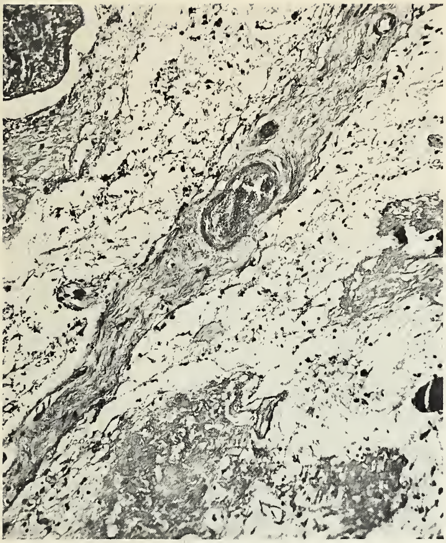


(c)

(c) The granule cells of the cerebellum are an ideal biological representation of the Bragg-peak concept of energy transfer in a monoenergetic particulate radiation system. The slow buildup of ionization terminates in a narrow zone of intense energy transfer as the particles rapidly lose momentum. The ratio of pyknotic to normal granular cell nuclei builds to a maximum and terminates in virtually a straight line.

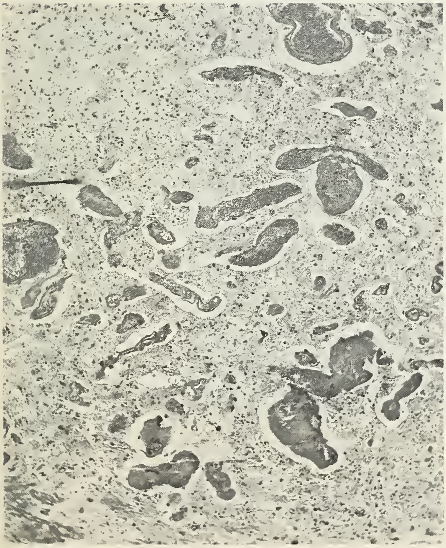
(a)

Fig. 12.4 Delayed radiation encephalopathy. (a) This photomicrograph illustrates some of the effects in greater detail. There is minimal fibrosis in the minor sulcus that transects this section, and the accompanying vessel displays little sclerosis at this point. There is some preservation of the fibrillar matrix of the molecular layer; however, the underlying cortex is almost totally necrotic. At the interface are a slight gliosis, telangiectasia, and small sclerotic arteries.



(b)

(c)

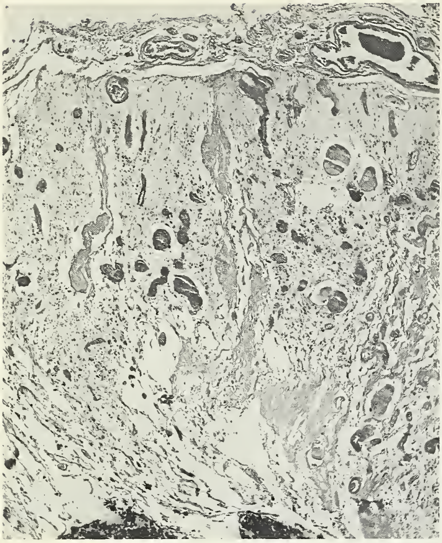


(d)

(b) The perivascular fibrosis that both broadens and obliterates the Virchow–Robin space is evident in this photomicrograph. The surrounding brain parenchyma shows severe spongy demyelination and degeneration, loss of nerve-cell population, and irregular areas of coagulation necrosis.

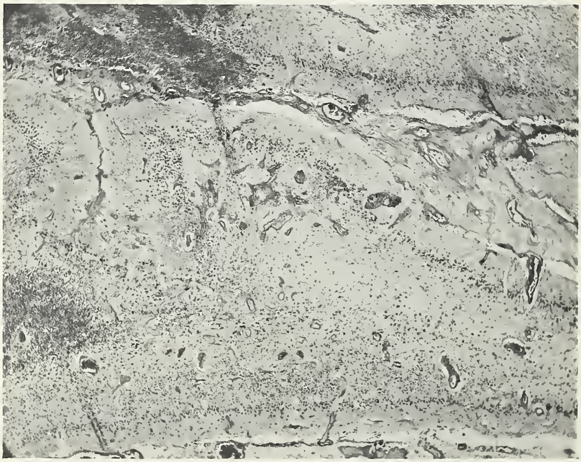
(c) Some of the degenerative foci have coalesced to form irregular cystic spaces. At the edge of such a space is a slight glial response. Small arteries with very thick walls and greatly constricted lumens are seen in this section. The left border shows a zone of identifiable brain parenchyma although demyelination is severe and there is diminution of the nerve-cell population.

(d) The delayed sequelae of irradiation frequently do not present a uniform response pattern. The degree of destruction and degeneration will vary throughout the zone of irradiation. Two important factors are the relative vascularity of the area involved and attenuation of total dose near the edge of the radiation field. This photomicrograph illustrates an area where some of the fibrillary and cellular composition of the brain substance is preserved although there is severe demyelination and telangiectasia.



(a)

Fig. 12.5 Delayed radiation encephalopathy. (a) This low-power photomicrograph illustrates radiation effects in the cerebral cortex of a young female who had received two courses of intense radiotherapy. The leptomeninges are fibrosed. The large veins do not exhibit appreciable thickening of their walls although the small arteries do. The molecular layer of the cortex retains some semblance of normal structure; however, the deeper layers present progressively severe degeneration. Telangiectasia and perivascular fibrosis of some of the penetrating vessels are present.



(b)

(b) The cerebellum received a substantial amount of radiation and responded with an almost total depopulation of the granule cells. This low-power photomicrograph shows portions of two fronds with the granular layer devoid of the characteristic closely packed cells. Some remnant of the line of Purkinje cells which separates the molecular and granular layers can be identified. There is marked increase in the connective tissues between the fronds, and this process also accompanies the penetrating vessels. Focal necrosis and hemorrhage are present.

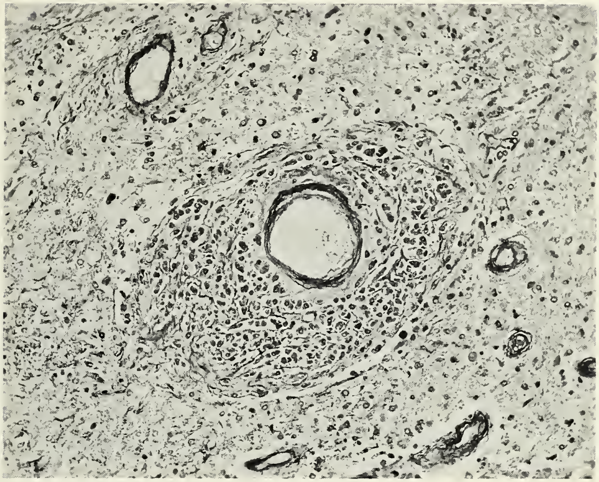


Fig. 12.6 Perivascular cell infiltrate. In some instances the early delayed radiation encephalopathy may invoke a limited inflammatory response presumably to the tissue destruction. This infiltration often appears most intense in the meninges overlying the parenchymal damage. This high-power photomicrograph shows a cross section through a penetrating pial vessel. The connective-tissue proliferation in the Virchow–Robin space has become fenestrated and infiltrated by lymphocytes and plasma cells extending down from the meninges. This leukocytic response may also show up along the edge of large necrotic foci.

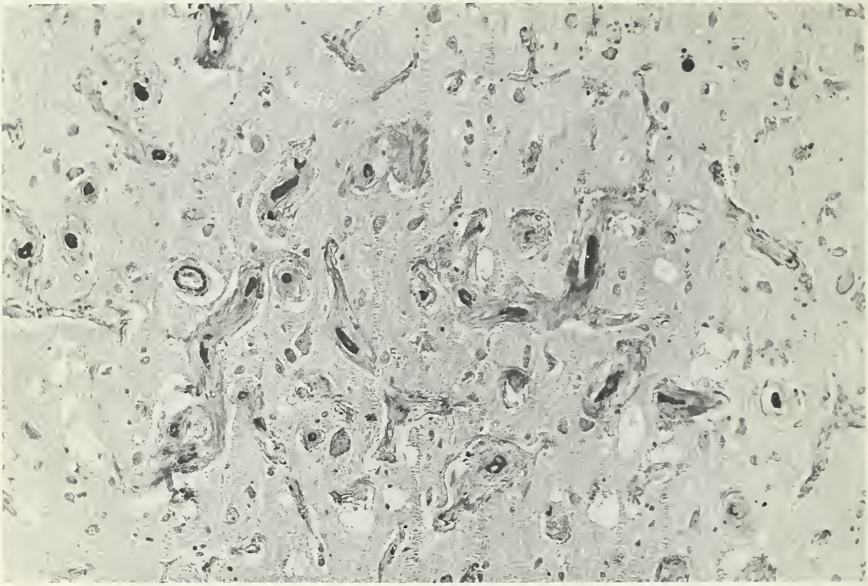


Fig. 12.7 **Late vascular changes in the brain.** Since the postirradiation survival extends beyond several months, some of the effects show stabilization although the fundamental injury—vascular sclerosis—insidiously progresses. In those areas not receiving the full thrust of the irradiation, parenchymal damage may attain a maximum and then level off. This photomicrograph shows an area with small foci of demyelination and moderate loss of nerve cells. The major feature, however, is the severe sclerotic change in the exaggerated vascular plexus. Deposits of calcium can be seen in the vessel walls.

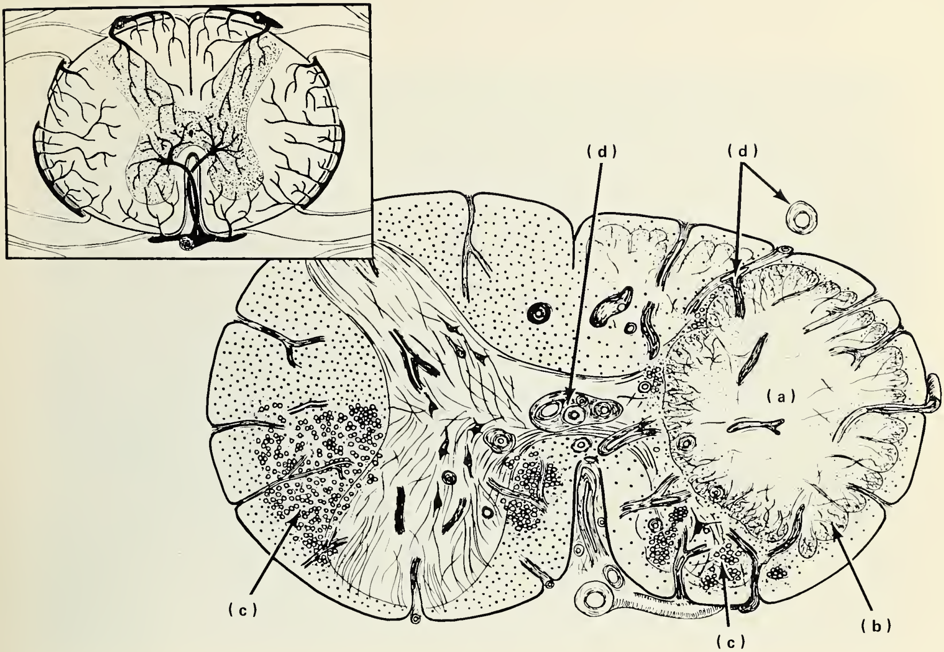
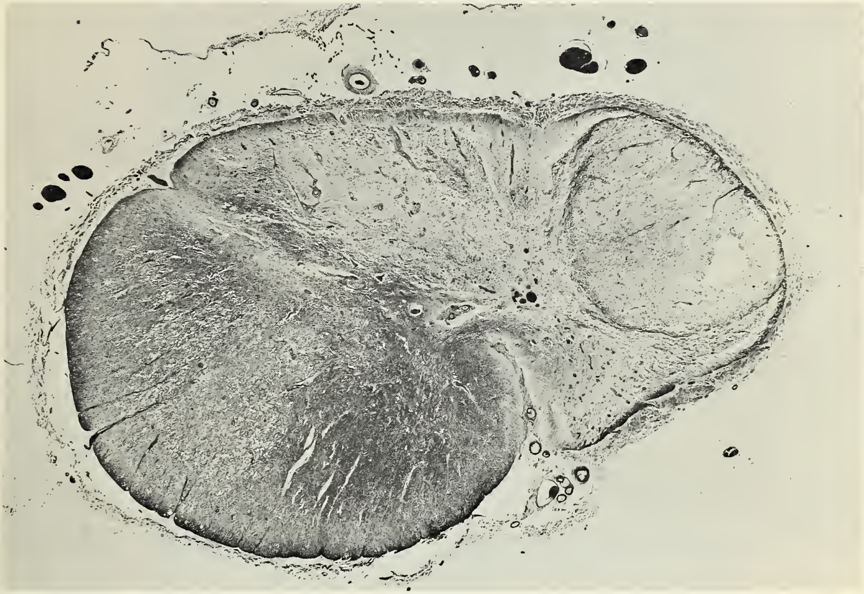


Fig. 12.8 Delayed radiation myelopathy. This schematic cross-sectional representation of the spinal cord illustrates some of the lesions associated with delayed radiation myelopathy. The inset demonstrates the principal arterial distribution with the anterior spinal artery and two posterior spinal arteries giving off circumferential and penetrating branches. The irradiated cord may at any one time present a diversity of effects in various phases of development. The right half of this section shows a large area of necrosis (a) through which pass sclerosed branches of the penetrating vessels. The edge of this lesion retains some of the fibrillar ground substance and a few glial cells. Within, but at the periphery of, the necrosis is a broad zone of "gitter" cells or foamy histiocytes (b). There are several moderately well demarcated foci of demyelination (c) depicting early stages in the development of necrosis. The vasculature is prominent (d), especially on the right side of the cord, owing to intimal and medial thickening and a marked increase in the perivascular connective tissue.

(a)

Fig. 12.9 Delayed radiation myelopathy. These two very low-power photomicrographs illustrate the diversity of the pathology associated with radiation-induced myelopathy. Almost all severe effects are related to vascular damage; and, as this process is characteristically random in site and time, the consequent degeneration follows no set pattern. There is, however, some conformity to specific areas of circulatory dependence.

(a) There is bilateral, almost symmetrical, necrosis of the posterior funiculi. The posterior columns are thinned and compressed in contrast to the near-normal appearance of the anterior columns. There is a well-defined area of demyelination in the left lateral funiculus, which in this section is to the right. The contralateral funiculus shows very early sponginess suggesting beginning myelin destruction.



(b)

(b) The most advanced necrosis is confined to the left lateral funiculus. The entire left side of the cord, however, is undergoing degeneration with most of the myelin and many of the nerve fibers gone. The left anterior and posterior columns are difficult to delineate. The nerve-cell population throughout this portion of the cord is severely diminished. There are some small glial cells and many foamy histiocytes. The thickened vessels can be seen traversing the area of parenchymatous degeneration. There is a rather well delineated area of early demyelination which seems to encompass the entire right lateral funiculus (left of section). The only elements of this cord seemingly uninvolved in this radiation myelopathy are the right columns and the tissue to the right of the anterior median fissure. Note the relative thickening of the meninges.

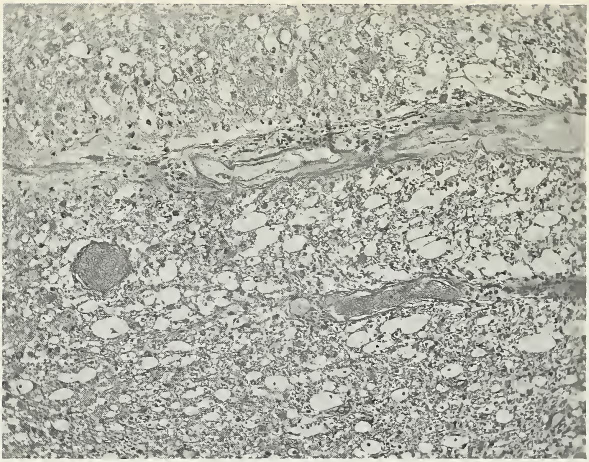
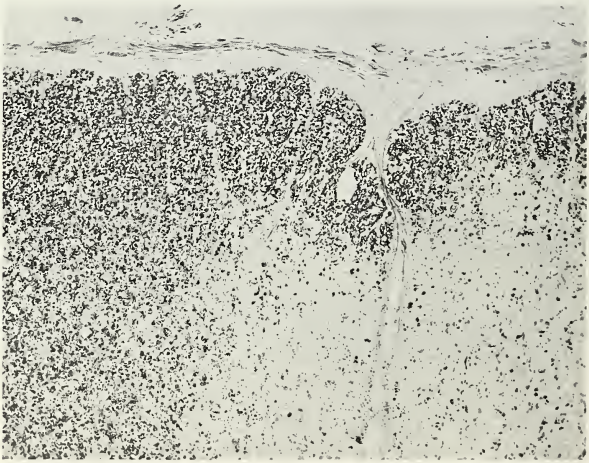
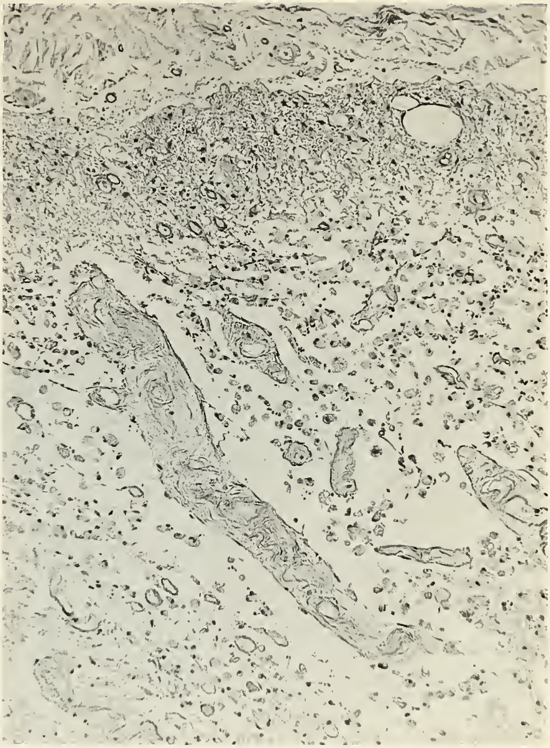


Fig. 12.10 Demyelination in radiation myelopathy. (a) Traversing this section is a small artery. Its wall shows plasmatic transudate and fibrinoid degeneration. There is an associated increase in perivascular connective tissue that is infiltrated by lymphocytes and plasma cells. The surrounding parenchyma has a spongy appearance denoting early demyelination and some fiber degeneration. Many nerve cells still remain.

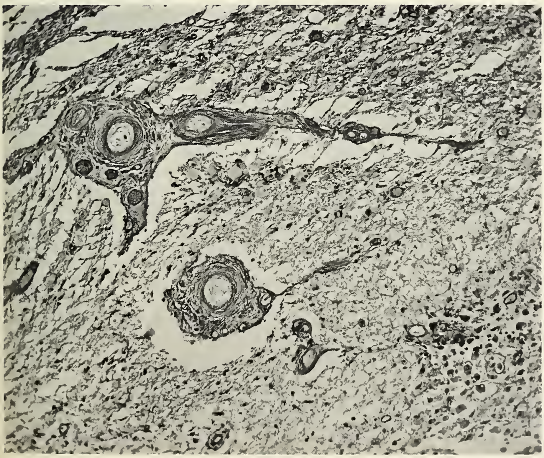


(b) This section has been specially stained to demonstrate myelin, which shows up as dark microcirclets encompassing the nerve-cell processes. There is almost total loss of myelin in the right lower quadrant with less destruction at the left edge. Beneath the pia–arachnoid is a zone of essentially normal myelination which reflects the presence of a rich superficial vascular plexus, which moderates the circulatory compromise in the deeper parenchyma.



(a)

Fig. 12.11 Late radiation myelopathy. (a) One of the characteristic lesions of late radiation myelopathy is the moderately well circumscribed focal necrosis. This high-power photomicrograph illustrates the periphery of such a lesion. The deeper portions are virtually devoid of any framework except for thick-walled vessels and a few discontinuous fibers. Cell debris and many gitter cells (histiocytes) are abundant. At the edge of the lesion there may be some degree of glial proliferation, which in this example is minimal. Note the narrow rim of subpial cord tissue that retains fundamental composition although exhibiting some degenerative effects. The meninges are thickened and fibrotic.



(b)

(b) Near the edge of the necrotic focus at the extreme lower right are two vascular channels seen in cross section. Both contain arteries and veins of various calibers, and the arteries are thickened by fibrinoid and fibrotic changes in the walls. All elements are encased in perivascular connective-tissue proliferation.

Notes

Notes